

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 38/00, C07K 5/12, 7/06, 7/08		A1	(11) International Publication Number: WO 97/10836
			(43) International Publication Date: 27 March 1997 (27.03.97)
(21) International Application Number: PCT/US96/15098 (22) International Filing Date: 20 September 1996 (20.09.96) (30) Priority Data: 08/531,525 21 September 1995 (21.09.95) US 60/004,091 21 September 1995 (21.09.95) US (71) Applicant: INNAPHARMA, INC. [US/US]; Suite 301, 10 Mountain View Road, Upper Saddle River, NJ 07458-1935 (US). (72) Inventors: HLAVKA, Joseph, J.; Tower Hill Road, Tuxedo Park, NY 10987 (US). PINCUS, Matthew, R.; 135 Eastern Parkway, Brooklyn, NY 11238 (US). NOBLE, John, Fowler; 67 Halley Drive, Pomona, NY 10970 (US). ABAJIAN, Henry, Baxter; 78 Plymouth Road, Hillsdale, NJ 07462 (US). KENDE, Andrew, S.; 19 Larchwood Drive, Pittsford, NY 14534 (US). (74) Agents: FERBER, Donna, M. et al.; Greenlee, Winner and Sullivan, Suite 201, 5370 Manhattan Circle, Boulder, CO 80303 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PEPTIDES AND PEPTIDOMIMETICS INHIBITING THE ONCOGENIC ACTION OF P21 RAS			
(57) Abstract <p>The present invention provides peptides, cyclized peptides and peptidomimetics which inhibit the oncogenic and/or transforming activity of the p21 <u>ras</u> protein, pharmaceutical compositions containing at least one of the <u>ras</u>-inhibiting peptides, cyclized peptides and peptidomimetics, and methods for inhibiting the <u>ras</u>-mediated oncogenic and/or transformation process in mammalian cells or tissues.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PEPTIDES AND PEPTIDOMIMETICS INHIBITING THE ONCOGENIC ACTION
OF P21 RAS

Field of the Invention

5 This invention relates to peptides effective in inhibiting
oncogenesis, particularly as related to inhibition of p21 ras and
adenocarcinomas of the colon, pancreatic carcinomas,
neuroblastomas, and other cancers which express the transformed
sequence of the ras gene product.

Background of the Invention

10 ras protooncogenes are activated by characteristic point
mutations in a wide variety of malignancies. The expressed p21
ras proteins are oncogenic by virtue of single substituted amino
acids, usually at position 12 or 61 of the 189-residue p21 ras
gene product. ras proteins act as membrane-associated molecular
15 switches that bind GTP and GDP and slowly hydrolyze GTP to GDP.

Mutations in ras are associated with the vast majority of
adenocarcinomas of the colon. Cancer of the colon is a highly
treatable and often curable disease when it remains localized to
the bowel. It is the second most frequently diagnosed malignancy
20 in the United States as well as the second most common cause of
cancer death. Surgery is the primary treatment and results in
cure in approximately 50% of patients. Adenocarcinoma is the
primary lesion in the majority of cases. Recurrence following
surgery is a major problem and often is the ultimate cause of
25 death. The prognosis for colon cancer patients is clearly
related to the degree of penetration of the tumor through the
bowel wall and the presence or absence of nodal involvement. For
locally advanced disease, the role of radiation therapy in colon
cancer is under clinical evaluation. There is no standard
30 therapy for advanced colon cancer and no evidence that
chemotherapy improves survival, although short-term palliation
may be achieved in approximately 10-20% of patients.

Pancreatic carcinoma has a high incidence of K-ras mutations. Mutated K-ras sequences which can be identified by polymerase chain reaction utilizing allele-specific primers can even be found in the plasma or serum from patients with pancreatic carcinoma. The c-Ki-ras oncogene is activated by point mutations involving codon 12 in 72%-100% of primary pancreatic adenocarcinomas, but the gene is not activated in nonneoplastic tissues. Cancer of the exocrine pancreas is rarely curable. The highest cure rate (4%-12%) occurs if the tumor is truly localized to the pancreas. Unfortunately, this stage of disease accounts for fewer than 20% of cases and, even with surgical resection, results in little more than a 5% 5-year survival rate. For small cancers (less than 2 cm) in the head of the pancreas with no lymph node metastases and no extension beyond the "capsule" of the pancreas, the survival rate following resection of the head of the pancreas approaches 20%. Overall survival rate of all stages is less than 2% at 5 years with most patients dying within one year. Worldwide, very few patients with cancers of the pancreatic tail or uncinate process have been cured.

Lung cancers also frequently involve ras mutations. Point mutations in codon 12 of the K-ras protooncogene occur more frequently in lung adenocarcinomas from smokers (30%) than they do in lung adenocarcinomas from nonsmokers (7%), suggesting that smoking is an important factor in the induction of these mutations. The ras oncogene may thus be a specific target of the mutagenic activity of tobacco smoke, and suggest that DNA alterations at this site can occur early and irreversibly during the development of adenocarcinomas of the lung.

Mutations in the ras protooncogenes are the most frequently observed molecular alteration in acute myeloid leukemia (AML). Whether ras mutations occur as late or relatively early events in the multistep process of myeloid transformation, remains an open question. There is significant evidence that the ras oncogene plays a role in experimental mammary carcinogenesis; the evidence in human breast cancer, however, is more limited.

Similarly, there is significant evidence that the ras oncogene plays a role in nitrosoamine-induced esophageal tumors in rats, but in human esophageal cancers ras gene mutations are more rarely found. However, it is probable that there is a significant role of mutated ras genes in both cell proliferation and malignant transformation of human esophageal cells.

Certain human neuroblastomas also show a high incidence of oncogenic ras mutations. Indeed, one study suggested that expressions of the oncogene N-myc and p21 together as detected by immunohistochemical staining could be among the most reliable prognostic indicators in neuroblastoma patients.

The ras proteins are key regulators of the growth of eukaryotic cells. Some of the direct targets are unknown. These target proteins include raf-1, gap, phosphatidylinositol-3-hydroxykinase and, very recently, two nuclear proteins, C-JUN and its kinase (JNK). The three-dimensional x-ray crystal structure for a ras-related protein bound to a domain of raf-1 has been elucidated. The ras-related protein (rak-1-a) binds to raf directly, utilizing residues contained in a sequence involving amino acids 35-37. All of the contact residues in the ras-related protein are homologous to those in the corresponding segment of ras-p-21. One of the inventors has shown that the p-21 ras protein (35-47 segment) selectively inhibits the mitogenic effects of oncogenic ras-p-21.

In addition to its role as an oncogene, the activation of ras proteins is a key step in the signal transduction pathways triggered by ligand-bound cell surface receptors, such as the insulin receptor.

The classical target of the ras protein is the GTPase activating protein GAP. This target protein is thought to play an essential role in the regulation of ras activity by increasing the GTPase activity of wild type, but not transformed ras. On the other hand, there is a considerable superfamily of these GAP-related proteins, which includes p120-GAP. Other target proteins besides mammalian gap itself include (1) IRA1 and IRA2, the functional equivalents of GAP in yeast. They regulate the ras-cyclic AMP pathway, controlling cell growth; (2) sar1, the

fission yeast protein that regulates ras1 in that organism; (3) BUD2, a yeast protein that activates BUD1/RSR1 which participates in the regulation of bud-site selection; (4) Human neurofibromatosis (gene NF1). NF1 is associated with type 1
5 neurofibromatosis, one of the most frequently inherited genetic diseases characterized, in part, by multiple neural tumors. NF1 has been shown genetically and biochemically to interact with and stimulate the GTPase activity of ras; (5) Drosophila Gap1, which acts as a negative regulator of signalling by the Sevenless
10 (SOS) receptor tyrosine kinase involved in eye development. Human SOS1 and SOS2 genes have also been recently identified which encode proteins that control GDP-->GTP exchange on ras proteins and are involved in signal transduction by tyrosine kinase receptors. *In situ* hybridization shows that SOS1 maps to
15 2p22-->p16 and SOS2 to 14q21-->q22 in the human genome.

Another important target of ras is raf. The protein encoded by the c-raf-1 protooncogene is thought to function downstream of p21 ras because disruption of raf blocks signalling by ras in a number of systems. A highly-conserved 81 residue region of the
20 N-terminus of raf protein has been to be shown to be critical as the ras protein interaction region. Importantly, the raf gene product interacts with both wild-type and activated ras protein. In one study, approximately 50% of the clones identified as interacting with ras were encoded portions of the c-raf and A-raf
25 serine/threonine kinases. Thus, ras and the N-terminal region of raf protein associate directly *in vitro* and this interaction is dependent on GTP bound to ras.

Within the superfamily of ras-related GTP-binding proteins, only the ras protein itself has been shown to act as an oncogenic
30 protein. Many other proteins, however, have substantial amino acid homology to ras. This ras superfamily of GTP-binding proteins (> 50 members) regulates a diverse spectrum of intracellular processes. These include cellular proliferation and differentiation, intracellular vesicular trafficking,
35 cytoskeletal control, NADPH oxidase function, as well as others. Some of these homologs may have biological activities which are related to ras. For example, rhoA encodes a ras-related

GTP-binding protein that was thought principally to play a role in cytoskeletal organization. Recent evidence, however, has suggested both that rhoA could act either as a dominant oncogene, since transfection of both normal and activated rho genes confer a transformed phenotype on fibroblast cells in culture, or as a recessive tumor suppressor gene, by virtue, in part, of its chromosomal location at 3p21, a site deleted in many human malignancies. Thus, it is important to consider these ras homologs as potentially involved in cell growth and transformation.

Azatyrosine strongly inhibits oncogenic ras-p-21. This small molecule induces the rrg gene, which encodes a proteinase sequence showing 90% amino acid sequence identity to lysyl oxidase.

To acquire transforming potential, the precursor of the ras oncoprotein must undergo farnesylation or similar modification of the cysteine residue located in a carboxyl-terminal tetrapeptide. These C-terminal lipid modifications are essential for the interaction of ras-related proteins with membranes. While all ras proteins are farnesylated and some palmitoylated, the majority of other ras-related proteins are geranylgeranylated. Thus selective peptide and peptidomimetic inhibitors of ras lipidation have found potential utility as anti-oncogenic agents.

In view of the foregoing, there is there a longfelt need in the art for agents which inhibit the transforming ability of ras. As described above, selective peptide and peptidomimetic inhibitors or ras lipidation have found potential utility as anti-oncogenic agents (Kohl et al. (1993) Science 260:1934-1937; James et al. (1993) Science 260:1937-1942). Similarly, FR patents 2694296 and 2690162 teach that peptides derived from the GAP protein may serve to inhibit ras. However, neither '694296 nor '690162 describes peptides derived from the ras protein itself. EP 203587 describes new ras oncogene polypeptides which are used for producing antibodies for immunogenic assays. However, these sequences are derived from ras and its homologs in the carboxyl terminal domain (residues 170 - 189 in SEQ ID

NO:5) and are thus physically distant from and completely unrelated to any sequences claimed herein. Furthermore, these sequences were claimed for the production of antibodies, preferably by linking to an immunogenic carrier, and a claim for
5 direct therapeutic application was not made.

Thus, peptides constructed from ras and its homologs for therapeutic application, namely by interfering with downstream or upstream actions of ras itself, are useful. Furthermore, the method of identification of said peptides utilizing calculational
10 approaches is believed novel and has unexpectedly led us to these cyclic peptides and peptidomimetics disclosed herein.

Summary of the Invention

The present invention provides peptides, cyclized peptides and peptidomimetics capable of inhibiting the oncogenic action
15 of p21 ras. The oncogenic ras-inhibiting cyclized peptides correspond to domains of the oncogenic ras protein which are most flexible and important in interacting with target proteins upstream and downstream from ras. The peptidomimetics are obtained by molecular modeling, including the structural
20 minimization techniques of molecular dynamics.

The peptides are designated by the formulas: Val-Val-Ile, Lys-Arg-Val, Ile-Lys-Arg-Val-Lys-Asp (SEQ ID NO:1), Lys-Cys-Asp-Leu-Ala (SEQ ID NO:2), Cys-Asp-Leu-Ala-Ala-Arg-Thr (SEQ ID NO:3), Asp-Leu-Ala-Ala (SEQ ID NO:4) or physiologically acceptable salts
25 of the foregoing peptides.

Also provided in the present invention are cyclic analogues of the above peptides and certain peptides and cyclic peptides:

cyclo [- R(1) R(2) Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp R(3) R(4) -] (I);

30 cyclo [-R(1) R(2) Val Val Ile R(3) R(4) -] (II);

cyclo [-R(1) R(2) Tyr Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro R(3) R(4) -] (III);

cyclo [-R(1) R(2) Lys Arg Val R(3) R(4)-] (IV);

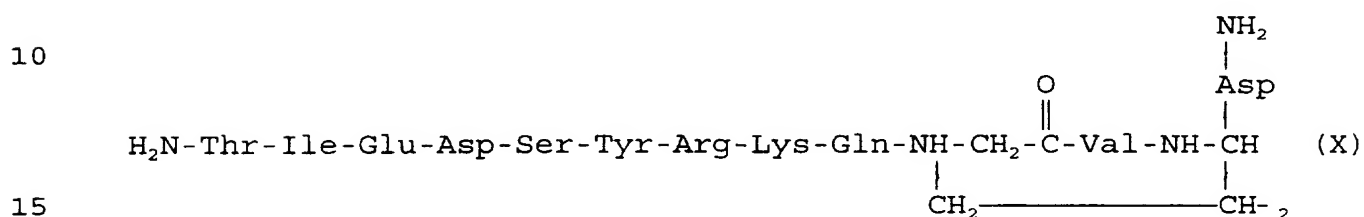
cyclo [-R(1) R(2) Ile Lys Arg Val Lys Asp R(3) R(4)-] (V);

cyclo [-R(1) R(2) Gly Asn Lys Cys Asp Leu Ala Ala Arg Thr
Val Glu R(3) R(4)-] (VI);

5 cyclo [-R(1) R(2) Lys Cys Asp Leu Ala R(3) R(4)-] (VII);

cyclo [-R(1) R(2) Cys Asp Leu Ala Ala Arg Thr R(3) R(4)]
(VIII);

cyclo [-R(1) R(2) Asp Leu Ala Ala R(3) R(4)-] (IX); and



or physiologically acceptable salts thereof.

In cyclized peptide formulas (I)-(IX), R(1) R(2), R(3) and R(4) represent, in the most general case, any amino acid which can serve as an amino acid residue linker. Amino acid residue
20 linkers are usually at least one residue and can be most often two to four residues, more often 1 to 10 residues, both ranges being inclusive. Typical amino acid residues useful for linking are tyrosine, cysteine, lysine, and glutamic and aspartic acid. Most preferably [R(1), R(2)] and [R(3), R(4)] are each
25 independently selected from either the group consisting of Glu, Gln, Asp, Asn or from the group consisting of Lys, Arg, Orn.

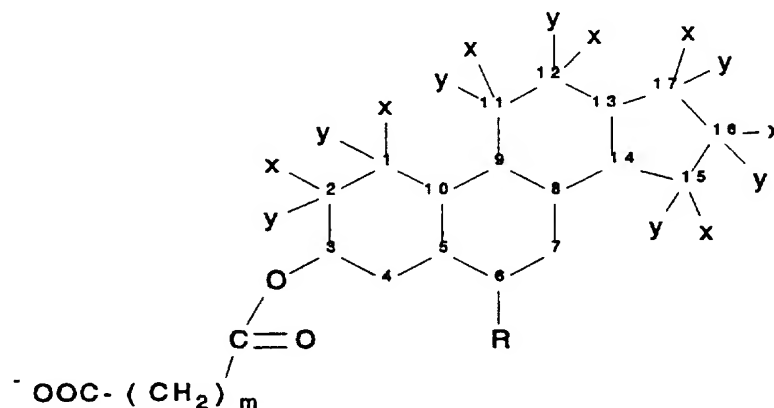
The symbol - represents a bond between the carboxyl and amino termini by which R(1) and R(4) can be interconnected to each other via an lower alkenyl or lower alkynyl group, but most
30 preferably by a branched or unbranched methylene bridge of type --(CH₂)_m--or --(CH₂)_m--M--(CH₂)_{m'}--. In such an moiety, m and m'

are integers from 1 to 6, inclusive, and preferably from 1 to 3, inclusive; and M is NH, N[R(5)], O, S or CH-R(5), wherein R(5) is lower alkyl, cycloalkyl or aryl and is preferably methyl, ethyl, propyl, phenyl, X-phenyl, or heterocyclic, wherein X is Cl-, CF₃-, F-, substituted at the o-, m-, or p- positions on the phenyl group M can contain a part of another diamino acid within the same peptide, e.g., the omega amino group of the one residue can be so linked to such an unnatural amino acid residue in a terminal residue.

Furthermore, any amino acid in the sequences provided hereinabove may be replaced with its D-analogue, with the proviso that not more than 50% of the total amino acids are so replaced. Similarly, a homologous conservative substitution for any amino acid is within the bounds of the present invention provided that substitution does not eliminate the oncogenic ras p21-inhibiting activity. Thus, depending on the applications for which the peptides according to the invention are intended, it is also possible to envisage intercalating between several amino acids, or even between all the amino acids, of the peptides defined above, dextrorotatory amino acids, and in particular dextrorotatory phenylalanine or dextrorotatory tryptophan, capable of preventing the action of the degradative enzymes in the cell environment and thus of increasing their activity. Another modification in this sense consists in replacing certain amino acids, for example of the isoleucine type, by leucine.

In addition, a subject polypeptide can differ, unless otherwise specified, from the natural sequences shown above by the sequence being modified by terminal -NH₂ acylation, e.g., acetylation, or by terminal-carboxylamidation, e.g., with ammonia, alkylamines, and the like.

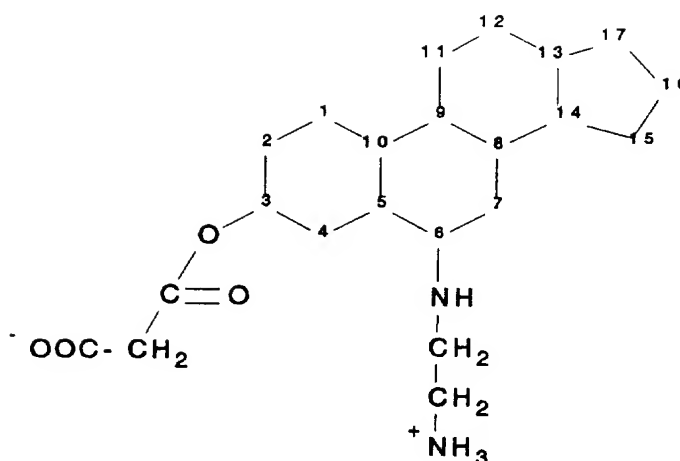
This invention further relates to peptidomimetics which model the critical semi-extended conformation of at least one peptide of or cyclic peptide of the present invention, exemplified by the compounds of Structure 1:



STRUCTURE 1

wherein the sidechain R attached at the carbon atom numbered 6 on the sterol nucleus can be $\text{NH-CH}_2\text{-CH}_2\text{NH}_3^+$, alkylamino, arylamino, or aralkylamino group, and wherein the sidechain attached at the carbon number 3 can be replaced with $-\text{O-C(=O)-}-(\text{CH}_2)_m\text{-COOH}$, where m is an integer from 1 to 6, inclusive, preferably from 1 to 3, inclusive, and more preferably 2, and one of X and Y at each position independently, can be one H, a small alkyl group of C_1 to C_3 , preferably C_1 ; a halogen, preferably F, or an amino group where the other of one of X and Y is H. Preferably, each of X and Y is H.

10



STRUCTURE 2

An exemplary compound falling within Structure 1 is 3 malonoxy-6-(2-aminoethyl)aminocyclopentanoperhydrophenanthrene (Structure 2).

5 Detailed Description of the Invention

The natural sequence of the human oncogenic ras p21 is given in SEQ ID NO:5. The crystal X-ray structure has been determined at high resolution for that portion of the human ras protein corresponding to residues 1 to 166 of SEQ ID NO:5.

10 The regions of the p21 protein that are the most likely to change their conformations upon activation of the protein, e.g. by oncogenic amino acid substitutions have been computed using two different methods. Both methods are based on the principle that the linear sequence of amino acids in a protein determines
 15 its unique three-dimensional structure. Given an amino acid sequence of a polypeptide or protein, therefore, it should be possible to predict its three-dimensional structure. This task can be accomplished by using the principle that the observed three-dimensional structure of a protein is the one of lowest
 20 free energy. There are a vast number of possible structures a given polypeptide chain can adopt, but essentially only one of these is observed. To allow folding to occur, therefore, the interatomic interactions in the protein chain must greatly

stabilize its final folded form, i.e., lower its conformational energy substantially with respect to that of any other competing structure. Thus, to compute the lowest energy form of a protein, it is necessary to be able first to compute the conformational energy of a given conformation of the protein and then, second, to generate its low energy conformations, or a representative sampling of them. The structure of lowest conformational energy so computed is then predicted to be the observed structure of the protein. This structure may be the one determined by x-ray crystallography or by 2- or 3-dimensional nuclear magnetic resonance (NMR) techniques.

A set of potential energy functions, in the computer program ECEPP (Empirical Conformational Energies of Peptides Program), have been developed that accurately compute the conformational energies of given conformations of proteins. The conformational energy of a peptide can be expressed in Equation 1.

$$E_{tot} = \sum_{i \neq j} \frac{Q_i Q_j}{DR_{ij}} + \sum_{i \neq j} \epsilon_{ij} \left(\left[\frac{\rho_{ij}}{R_{ij}} \right]^{12} - 2 \left[\frac{\rho_{ij}}{R_{ij}} \right]^6 \right) + \sum_k \left(\frac{A_k}{2} \right) (1 \pm \cos(n\theta_k))$$

where E_{tot} is the total conformational energy of the protein, the Q 's are the charges on the i^{th} and j^{th} atoms; R_{ij} is the distance between the i^{th} and j^{th} atoms, D is the dielectric constant, ϵ_{ij} and ρ_{ij} are the lowest non-bonded (Lennard-Jones) energy and the distance at this lowest energy between atoms i and j in the protein; A_k is the torsional barrier to rotation around specific bonds; θ_k is the k^{th} dihedral angle in the protein; n is a degeneracy factor, i.e., 3 for single bonds and 2 for double bonds; and the sign in the last summation term is positive for single bonds and negative for double bonds such as occur in the peptide bond units.

This equation shows the total conformational energy as the sum of three terms: the pairwise electrostatic interactions between the individual atoms of a protein, each of which has a partial charge, (first sum); a non-bonded energy term (second term) that consists of an attractive term that varies as the

inverse sixth power (tenth power for hydrogen-bonding atoms) of the distance between the atoms (from an induced dipole-induced dipole interaction term) and a repulsive term, from the overlap of electron shells, that varies as the inverse twelfth power of the interatomic distance; and finally a torsional term (third sum) that depends upon the bonds about which rotation takes place. All of the constants in these terms have been determined from experimental crystal packing data and reproduce the lattice constants of all of the crystal structures of small molecules to which they have been applied and, where measured, the sublimation energies of these crystals. These potential functions have been used to compute the low energy minima for single terminally blocked amino acid residues, simple peptides, oligopeptides, polypeptides, and proteins with excellent agreement between the lowest energy predicted structures and the structures determined experimentally. These potentials have therefore been well-tested, are based on experimental data, and have proved to be reliable in prediction of structure from sequence.

These potential functions have been used to compute the average structure for the ras-p-21 protein in its normal and in its oncogenic form using the perturbation method called the electrostatically-driven Monte Carlo method (EDMC). Specific regions of the oncogenic p21 protein undergo large conformational changes compared with the structure of the normal, inactive protein. One of these regions has been found to be residues 35-47. All of the segments that change conformation in the oncogenic protein were found to be the most flexible in the normal, inactive protein.

Of considerable significance has been the finding that a completely different method, viz. molecular dynamics, based upon a completely different set of potential functions, i.e. the program DISCOVER, yields identical results for the p21 protein.

Molecular dynamics is based on the principle that the positions of the atoms of a molecule can be predicted as a function of time by solving Newton's equations of motion for the molecule. The force on the molecule is the negative of the first derivative of the potential function with respect to the

coordinates of each of the atoms. Newton's equations of motion are then integrated, using the Verlet algorithm, over a trajectory such that the low energy regions around the starting structure are computed. The trajectories are computed over time intervals such that the total energy converges to a low, constant value. The structures whose energies have converged are then used to compute an average structure. Comparison of the coordinates of the atoms of this average structure with those of the starting structure reveals regions of the protein whose conformations may change significantly. Furthermore, if the variance of the coordinates of regions of the low energy structures from the corresponding coordinates of the average structure are high, these regions can be identified as being flexible, i.e., are the ones most likely to be parts of effector domains. Within this algorithm, for the p21 protein, up to 2000 water molecules have been generated around the protein in the molecular dynamics simulations performed thus far.

Using these novel calculational approaches, the present inventors have identified important peptide regions of the protein that are involved in the signal transduction process, and these peptides can be used to design anti-cancer agents, as taught herein. We have found that most particularly the 35-47, 96-110 and 115-126 peptides have strong and specific anti-oncogenic p21 activity. Even more particularly, we found that these domains contain unique extended structures and/or short beta-bend structures which are hypothesized to account in large part for their biological uniqueness. This suggested that cyclization of the peptide structures to force the beta-bend conformation in place would serve to enhance therapeutic activity.

The results of these studies indicate that a domain of particular interest is the domain from residues 35 through 47 of SEQ ID NO:5, i.e., Thr-Ile-Glu-Asp-Ser-Tyr-Arg-Lys-Gln-Val-Val-Ile-Asp (SEQ ID NO:6), of even more particular interest the peptide corresponding to residues 44 to 46 in SEQ ID NO:5, i.e., Val-Val-Ile, of still more interest is the sequence from residues 96 to 110 of SEQ ID NO:5, i.e., Tyr-Arg-Glu-Gln-Ile-Lys-Arg-Val-

Lys-Asp-Ser-Asp-Asp-Val-Pro (SEQ ID NO:7), of even more particular interest is the sequence from residues 101-103 in SEQ ID NO:5, i.e., Lys-Arg-Val; and the sequence corresponding to residues 100 to 105 in SEQ ID NO:5, i.e., Ile-Lys-Arg-Val-Lys-Asp (SEQ ID NO:1); the sequence corresponding to residues 115 to 126 of SEQ ID NO:5, i.e., Gly-Asn-Lys-Cys-Asp-Leu-Ala-Ala-Arg-Thr-Val-Glu (SEQ ID NO:8); and most particularly the sequence corresponding to residues 117 to 121 of SEQ ID NO:5, i.e., Lys-Cys-Asp-Leu-Ala (SEQ ID NO:2) and the sequence corresponding to residues 118 to 124 of SEQ ID NO:5, i.e., Cys-Asp-Leu-Ala-Ala-Arg-Thr (SEQ ID NO:9); and the sequence corresponding to residues 119 to 122 of SEQ ID NO:5, i.e., Asp-Leu-Ala-Ala (SEQ ID NO:4).

Additional sequences homologous to the various preferred sequences recited hereinabove can be derived by one skilled in the art from the sequences of closely related ras proteins. Such sequences may possess enhanced therapeutic activity. Nonlimiting examples of such proteins closely related to the ras gene product which represent the parent sequences having identical or nearly identical three dimensional structures and from which homologs of the sequences given in the preceding paragraph can be derived by one normally skilled in the art are:

ras-related protein Ara-3 [Arabidopsis thaliana (mouse ear cress)] (SEQ ID NO:10);

ras-related protein Ara-2 [A. thaliana] SEQ ID NO:11;

25 ras-related protein Ara-1 [A. thaliana] SEQ ID NO:12;

ras-related protein OraB-1 [Discopyge ommata (electric ray)] SEQ ID NO:13;

ras-related protein Rab-1A [Lymnea stagnalis (great pond snail)] SEQ ID NO:14;

ras-related protein Rab-2 [Homo sapiens (human)] SEQ ID NO:15;

ras-related protein Rab-2 [L. stagnalis] SEQ ID NO:16;

ras-related protein Rab-2 [Oryctolagus cuniculus (rabbit)]
5 SEQ ID NO:17;

ras-related protein Rab-2 [Rattus norvegicus (rat)] SEQ ID NO:18;

ras-related protein Rab-3 [Drosophila melanogaster (fruitfly)] SEQ ID NO:19;

10 ras-related protein Rab-4 [R. norvegicus] SEQ ID NO:20;

ras-related protein Rab-6 [Caenorhabditis elegans] SEQ ID NO:21;

ras-related protein Rab-6 [H. sapiens] SEQ ID NO:22;

15 ras-related protein Rab-7 [Canis familiaris (dog)] SEQ ID NO:23;

ras-related protein Rab-7 [Dictyostelium discoideum (slime mold)] SEQ ID NO:24;

ras-related protein Rab-8 [C. familiaris] SEQ ID NO:25;

ras-related protein RabC [D. discoideum] SEQ ID NO:26;

20 ras-related protein Rac-1 [C. elegans] SEQ ID NO:27;

ras-related protein Rac-1A [D. discoideum] SEQ ID NO:28;

ras-related protein RacB [D. discoideum] SEQ ID NO:29;

- ras-related protein RacC [D. discoideum] SEQ ID NO:30;
- ras-related protein Ral-A [H. sapiens] SEQ ID NO:31;
- ras-related protein Ral-B [H. sapiens] SEQ ID NO:32;
- ras-related protein O-Ral [D. ommata] SEQ ID NO:33;
- 5 ras-related protein Ora-1 [D. ommata] SEQ ID NO:34;
- ras-related protein Ora-2 [D. ommata] SEQ ID NO:35;
- ras-related protein Ora-3 [D. ommata] SEQ ID NO:36;
- ras-related protein Rap-1 [D. discoideum] SEQ ID NO:37;
- ras-related protein Rap-2A [H. sapiens] SEQ ID NO:38;
- 10 ras-related protein Rap-2B [H. sapiens] SEQ ID NO:39;
- ras-related protein O-KREV [D. ommata] SEQ ID NO:40;
- ras-related protein Rap-1A [H. sapiens] SEQ ID NO:41;
- ras-related protein Rap-1B [H. sapiens] SEQ ID NO:42;
- ras-like protein GNROR3 [D. melanogaster] SEQ ID NO:43;
- 15 ras-like protein rasA [D. discoideum] SEQ ID NO:44;
- ras-like protein rasB [D. discoideum] SEQ ID NO:45;
- ras-like protein rasC [D. discoideum] SEQ ID NO:46;
- ras-like protein rasG [D. discoideum] SEQ ID NO:47;
- ras-like protein F54C8.5 [C. elegans] SEQ ID NO:48;

ras-like protein CC-ras [Coprinus cinereus (inky cap fungus)]

SEQ ID NO:49;

ras-like protein [Geodia cydonium (sponge)] SEQ ID NO:50;

5 ras-related protein Rab-10 [C. familiaris] SEQ ID NO:51;

ras-related protein Rab-11 [H. sapiens] SEQ ID NO:52.

10 In addition, as described hereinabove, the therapeutic activity of these sequences is enhanced by cyclization. Cyclization forces and maintains the conformations of these peptides in unique structures like beta-bends. The following are representative, nonlimiting examples of cyclized peptides useful for inhibiting the oncogenic activity of the ras protein, said peptides having formulas as given below:

15 cyclo [- R(1) R(2) THR ILE GLU ASP SER TYR ARG LYS GLN VAL VAL ILE ASP R(3) R(4)-] (I)

cyclo [-R(1) R(2) VAL VAL ILE R(3) R(4)-] (II)

cyclo [-R(1) R(2) TYR ARG GLU GLN ILE LYS ARG VAL LYS ASP SER ASP ASP VAL PRO R(3) R(4)-] (III)

cyclo [-R(1) R(2) LYS ARG VAL R(3) R(4)-] (IV)

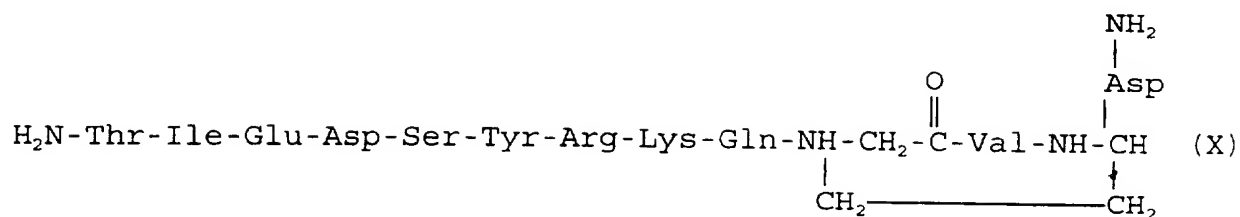
20 cyclo [-R(1) R(2) ILE LYS ARG VAL LYS ASP R(3) R(4)-] (V)

cyclo [-R(1) R(2) GLY ASN LYS CYS ASP LEU ALA ALA ARG THR VAL GLU R(3) R(4)-] (VI)

cyclo [-R(1) R(2) LYS CYS ASP LEU ALA R(3) R(4)-] (VII)

cyclo [-R(1) R(2) CYS ASP LEU ALA ALA ARG THR R(3) R(4)-] (VIII)

cyclo [-R(1) R(2) ASP LEU ALA ALA R(3) R(4)-] (IX); and



or a physiologically acceptable salt thereof.

In the aforementioned cyclized peptide formulas I-IX, R(1) R(2), R(3) and R(4) represent, in the most general case, any amino acid, such that they serve as amino acid residue linkers. Amino acid residue linkers are usually at least one residue and can be most often two to four residues, more often 1 to 10 residues. Typical amino acid residues used for linking are tyrosine, cysteine, lysine, glutamic and aspartic acid. Most preferably [R(1), R(2)] and [R(3), R(4)] independently are selected from either the groups [Glu, Gln, Asp, Asn] or [Lys, Arg, Orn].

The term - represents a bond between the carboxyl and amino termini by which R(1) and R(4) can be interconnected to each other via an lower alkyl, alkenyl or lower alkynyl group, but most preferably by a branched or unbranched methylene bridge of type --(CH₂)_m--or --(CH₂)_m--M--(CH₂)_{m'}--. In such an moiety, m and m' are integers from 1 to 6, inclusive, and preferably from 1 to 3, inclusive; and M is NH, N[R(5)], O, S or CH-R(5), wherein R(5) is lower alkyl, cycloalkyl or aryl and is preferably methyl, ethyl, propyl, phenyl, X-phenyl, or heterocyclic, wherein X is Cl-, CF₃, F-, substituted at the o-, m-, or p- positions on the phenyl group. M can contain a part of another diamino acid within the same peptide, e.g., the omega amino group of the one residue can be so linked to such an unnatural amino acid residue in a terminal residue.

Furthermore, any amino acid in the cyclized peptide sequences (I)-(X) recited herein may be replaced with its D-analogue, insofar as not more than 50% of the total amino acids

are so replaced. Similarly, a homologous conservative substitution for any amino acid is within the bounds of the present invention. Conservative substitutions include Glu for Asp, Gln for Asn and Val for Ile, among others, as well-known to the art. Depending on the applications for which the peptides according to the invention are intended, it is also possible to intercalate between several amino acids, or even between all the amino acids, of the peptides defined above, dextrorotatory amino acids, and in particular dextrorotatory phenylalanine or dextrorotatory tryptophan, capable of preventing the action of the degradative enzymes in the cell environment and thus of increasing their activity. Another modification in this sense consists in replacing certain amino acids, for example of the proline type, by D-tryptophan.

In addition, a subject polypeptide can differ, unless otherwise specified, from any of the natural sequences shown herein above by the sequence being modified by terminal $-NH_2$ acylation, e.g., acetylation, or by terminal-carboxylamidation, e.g., with ammonia, alkylamines, and the like.

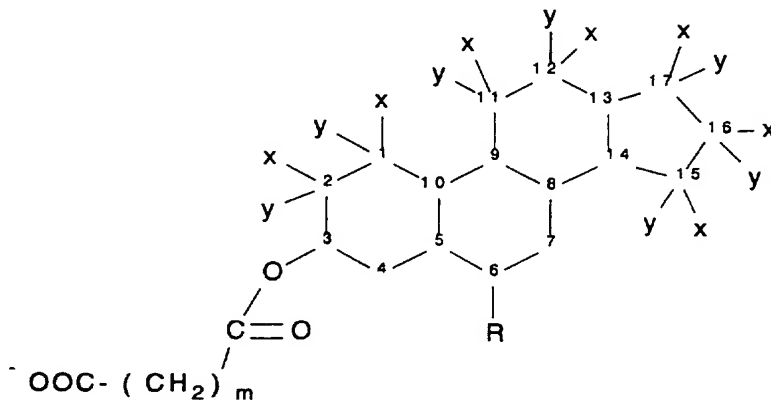
The placement of hydrophobic amino acid residues is highly dependent on the peptide sequence. For example, for the 35-47 peptide sequence, corresponding to amino acids 35-47 of SEQ ID NO:5, there is a distinct hydrophobic region for the amino acid residues corresponding to amino acids 44-46 of SEQ ID NO:5. The bridge in Compound (X) occurs at what corresponds in structure to amino acids 44-46 in SEQ ID NO:5. It is possible to extend this hydrophobic segment without sacrificing activity. For example, the carboxyl terminal Asp residue can be replaced with one or more hydrophobic residues such as Val or Ile, and the result is greater efficiency in crossing cell membranes.

Short half-lives of peptides, a major problem, can be at least partially extended by the addition of D-amino acids to either or both of the amino and carboxyl terminal ends of the peptide. These D-amino acid residues block the action of exo-proteases that degrade peptides from their amino or carboxyl ends. In addition, the cyclization of the peptide further renders the peptide less susceptible to proteolysis.

Recent advances in the field of peptides have been directed towards the stabilization of these peptides against enzymatic or hydrolytic degradation. It would be extremely valuable to stabilize these peptides from degradation by proteolytic enzymes in order to improve their pharmacokinetic properties. Enhanced resistance to enzymatic degradation would increase the usefulness of these peptides as therapeutic agents. However, since they only exhibit short half lives *in vivo*, large amounts of such peptides must typically be administered to a subject in order to achieve the desired effect. Alternatively, smaller quantities may be prescribed to an individual, but more frequent dosages would be required to achieve the same level of potency.

It is further well-known to those normally skilled in the art that it is possible to replace peptides with peptidomimetics. Peptidomimetics are generally preferable as therapeutic agents to peptides owing to their enhanced bioavailability and relative lack of attack from proteolytic enzymes. The present inventors have used the techniques of molecular modeling *supra* to design a peptidomimetic which mimics the critical beta-bend aspects of the peptide corresponding in sequence to amino acids 96-110 of SEQ ID NO:5 (p21 ras). The bend structure occurs at amino acids 102-103 in the p21 ras protein. These residues have been implicated in the binding of ras p21 to SOS.

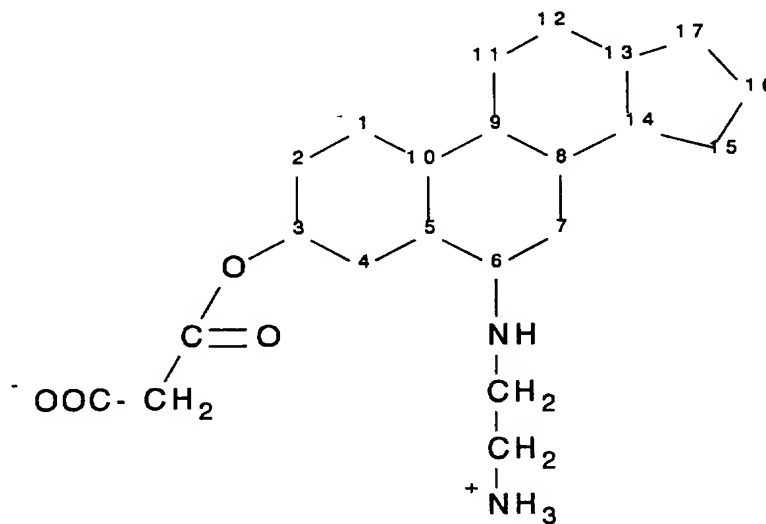
Peptidomimetic compounds which inhibit the oncogenic or transforming activity of the p21 ras protein are provided by the compounds of Structure I:



STRUCTURE I

wherein the sidechain R attached at the carbon atom numbered 6 on the sterol nucleus can be $\text{NH-CH}_2\text{-CH}_2\text{NH}_3^+$, alkyl amino, arylamino, or aralkylamino group, and wherein the sidechain attached at the carbon number 3 can be replaced with $-\text{O-C(=O)-}-(\text{CH}_2)_m\text{-COOH}$, where m is an integer from 1 to 6, inclusive, preferably from 1 to 3, inclusive, and more preferably 2, and one of x and y at each position independently, can be one H, a small alkyl group of C_1 to C_3 , preferably C_1 ; a halogen, preferably F, or an amino group where the other of one of x and y is H. Preferably, each of x and y is H.

Without wishing to be bound by any particular theory, the structure believed to be the optimally designed ras-inhibiting peptidomimetic is illustrated below in Structure II:



STRUCTURE 2

The instant invention comprises novel peptides of medicinal importance most particularly for the treatment of adenocarcinomas of the colon, pancreatic carcinomas, neuroblastomas, and other cancers of undefined germ cell origin which express the transformed sequence of the ras protein. These peptide sequences were unexpectedly obtained by the use of molecular dynamic simulations on ras p21 to define which domains of the protein

were most flexible and were thus most important in interacting with target proteins upstream and downstream from ras. These peptides are identified by the following amino acid sequences:
Thr-Ile-Glu-Asp-Ser-Tyr-Arg-Lys-Gln-Val-Val-Ile-Asp (SEQ ID NO:6), Val-Val-Ile, Tyr-Arg-Glu-Gln-Ile-Lys-Arg-Val-Lys-Asp-Ser-Asp-Asp-Val-Pro (SEQ ID NO:7), Lys-Arg-Val, Ile-Lys-Arg-Val-Lys-Asp (SEQ ID NO:1), Gly-Asn-Lys-Cys-Asp-Leu-Ala-Ala-Arg-Thr-Val-Glu (SEQ ID NO:8), Lys-Cys-Asp-Leu-Ala (SEQ ID NO:2), Cys-Asp-Leu-Ala-Ala-Arg-Thr (SEQ ID NO:9), and Asp-Leu-Ala-Ala (SEQ ID NO:4).

Including the cyclic analogues of the above peptides, namely:

cyclo [- R(1) R(2) Thr-Ile-Glu-Asp-Ser-Tyr-Arg-Lys-Gln-Val-Val-Ile-Asp-R(3) R(4)-] (I);

cyclo [-R(1) R(2) Val-Val-Ile-R(3) R(4)-] (II);

cyclo [-R(1) R(2) Tyr-Arg-Glu-Gln-Ile-Lys-Arg-Val-Lys-Asp-Ser-Asp-Asp-Val-Pro-R(3) R(4)-] (III);

cyclo [-R(1) R(2) Lys-Arg-Val R(3) R(4)-] (IV);

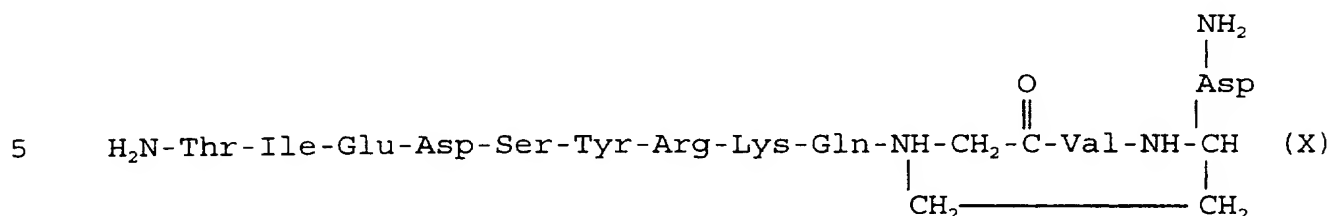
cyclo [-R(1) R(2) Ile-Lys-Arg-Val-Lys-Asp R(3) R(4)-] (V);

cyclo [-R(1) R(2) Gly-Asn-Lys-Cys-Asp-Leu-Ala-Ala-Arg-Thr-Val-Glu R(3) R(4)-] (VI);

cyclo [-R(1) R(2) Lys-Cys-Asp-Leu-Ala R(3) R(4)-] (VII);

cyclo [-R(1) R(2) Cys-Asp-Leu-Ala-Ala-Arg-Thr R(3) R(4)-] (VIII);

cyclo [-R(1) R(2) Asp-Leu-Ala-Ala R(3) R(4)-] Z (IX); and



or a physiologically acceptable salt thereof.

10 Wherein for cyclized peptide formulas designated by (I) - (IX) hereinabove, R(1) R(2), R(3) and R(4) represent, in the most general case, any amino acid, such that they serve as amino acid residue linkers. Amino acid residue linkers are usually at least one residue and can be most often two to four residues, more often 1 to 10 residues. Typical amino acid residues used for linking are tyrosine, cysteine, lysine, glutamic and aspartic acid, or the like. Most preferably [R(1), R(2)] and [R(3), R(4)] independently are selected from either the groups [Glu, Gln, Asp, Asn] or [Lys, Arg, Orn].

20 The symbol - represents a bond between the carboxyl and amino termini by which R(1) and R(4) can be interconnected to each other via an lower alkenyl or lower alkynyl group, but most preferably by a branched or unbranched methylene bridge of type --(CH₂)_m--or --(CH₂)_m--M--(CH₂)_{m'}--. In such an moiety, m and m' are integers from 1 to 6 and preferably from 1 to 3; and M is NH, N[R(5)], O, S CH-R(5) or does not exist, wherein R(5) is lower alkyl, cycloalkyl or aryl and is preferably methyl, ethyl, propyl, phenyl, X-phenyl, or heterocyclic, wherein X is Cl-, CF₃-, F-, substituted at the o-, m-, or p- positions on the phenyl. M can contain a part of another diamino acid within the same peptide, e.g., the omega amino group of the one residue can be so linked to such an unnatural amino acid residue in a terminal residue.

30 Furthermore, any amino acid in the sequences provided may be replaced with its D-analogue, insofar as not more than 50% of the total amino acids are so replaced. Conservative substitutions include Glu for Asp, Gln for Asn and Val for Ile, among others, as is well known to those of ordinary skill in the

art. Similarly, a homologous conservative substitution for any amino acid is within the bounds of the present invention. Depending on the applications for which the peptides according to the invention are intended, it is also possible to envisage
5 intercalating between several amino acids, or even between all the amino acids, of the peptides defined above, dextrorotatory amino acids, and in particular dextrorotatory phenylalanine or dextrorotatory tryptophan, capable of preventing the action of the degradative enzymes in the cell environment and thus of
10 increasing their activity. Another modification in this sense consists in replacing certain amino acids, for example of the proline type, by D-tryptophan.

In addition, a subject polypeptide can differ, unless otherwise specified, from the natural sequences shown above by
15 the sequence being modified by terminal -NH_2 acylation, e.g., acetylation, or by terminal-carboxylamidation, e.g., with ammonia, alkylamines, and the like.

The instant invention also comprises a method of use of the peptides *supra* for the treatment of adenocarcinomas of the colon,
20 pancreatic carcinomas, neuroblastomas, and other cancers of undefined germ cell origin which express the transformed sequence of the ras protein.

It is also an object of the present invention to provide peptides and cyclized peptide homologs from the sequences listed
25 in SEQ ID NOS:10-52.

The amino acid residues described herein are preferred to be in the "L" isomeric form. However, residues in the "D" isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property is retained by the
30 polypeptide. NH_2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxyl group present at the carboxy terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in J. Biol. Chem. 243:3552-3559 (1969) and adopted at 37 C.F.R.
35 1.822(b) (2)), The list of variable amino acids, capable of participating in the composition of this peptide is as follows: Y, Tyr, tyrosine; G, Gly, glycine; F, Phe, phenylalanine; M, Met,

methionine; A, Ala, alanine; S, Ser, serine; I, Ile, isoleucine; L, Leu, leucine; T, Thr, threonine; V, Val, valine; P, Pro, proline; K, Lys, lysine; H, His, histidine; Q, Gln, glutamine; E, Glu, glutamic acid; W, Trp, tryptophan; R, Arg, arginine; D, Asp, aspartic acid; N, Asn, asparagine; C, Cys, cysteine.

Amino acid residue sequences are presented herein in the conventional left-to-right direction of amino-terminus to carboxy-terminus. In addition, the phrase "amino acid residue" is broadly defined to include the amino acids listed hereinabove, and modified and unusual amino acids, such as those listed in 37 C.F.R. 1.822(b)(4), incorporated herein by reference. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates either a peptide bond to a further sequence of one or more amino acid residues or a covalent bond to an amino or hydroxyl end group.

Polypeptide and peptide are terms used interchangeably herein to designate a linear series of amino acid residues connected one to the other by peptide bonds between the alpha-amino and carboxy groups of adjacent residues.

Protein is a term used herein to designate a linear series of greater than about 20 amino acid residues connected one to the other as in a polypeptide.

The term synthetic peptide refers to a chemically produced chain of amino acid residues linked together by peptide bonds that is free of naturally occurring proteins and fragments thereof. The term peptide encompasses linear and cyclic peptides.

(D,L), (D), or (L) preceding the amino acid designation means that this amino acids exists in that specific isomeric form, i.e. (D,L) Phe means that the amino acid phenylalanine exists as a racemic mixture; (D) Phe or D-Phe means that the amino acid phenylalanine exists as the D-stereoisomer or implied R configuration; (L) Phe means that the amino acid phenylalanine exists as the L stereoisomer or implied S configuration.

Alkyl as used herein means methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl,

neopentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl,
1,1-dimethylpropyl, n-hexyl, 1-methylpentyl, 2-methylpentyl,
3-methylpentyl, 4-methylpentyl, 3,3-dimethylbutyl,
2,2-dimethylbutyl, 1,1-dimethylbutyl, 2-ethylbutyl, 1-ethylbutyl,
5 1,3-dimethylbutyl, n-heptyl, 5-methylhexyl, 4-methylhexyl,
3-methylhexyl, 2-methylhexyl, 1-methylhexyl, 3-ethylpentyl,
2-ethylpentyl, 1-ethylpentyl, 4,4-dimethylpentyl,
3,3-dimethylpentyl, 2,2-dimethylpentyl, 1,1-dimethylpentyl,
n-octyl, 6-methylheptyl, 5-methylheptyl, 4-methylheptyl,
10 3-methylheptyl, 2-methylheptyl, 1-methylheptyl, 1-ethylhexyl,
1-propylpentyl, 3-ethylhexyl, 5,5-dimethylhexyl,
4,4-dimethylhexyl, 2,2-diethylbutyl, 3,3-diethylbutyl,
1-methyl-1-propylbutyl.

Cycloalkyl refers to a hydrocarbon ring having from 3 to 7
15 carbon atoms, inclusive. Examples of cycloalkyl groups are
cyclopropyl, cyclopentyl, cycloheptyl, cyclooctyl, cyclononyl,
and the like.

The term aryl refers to aromatic groups which have at least
one ring having a conjugated pi electron system and includes
20 carbocyclic aryl, heterocyclic aryl, aralkyl, and biaryl groups,
all of which may be optionally substituted.

Heterocyclic groups means groups having from 1 to 3
heteroatoms as ring atoms in the aromatic ring and the remainder
of the ring atoms carbon atoms. Suitable heteroatoms include
25 oxygen, sulfur, and nitrogen, and their heterocyclic compounds
can include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl
pyrrolo, pyrimidyl, pyrazinyl, imidazolyl, and the like, all
optionally substituted.

Substituted heterocyclic refers to any heterocyclic aryl
30 group substituted by a alkyl, aryl, cycloalkyl, halo, sulfonate,
or trifluoromethyl group.

The term alkyl amino refers to the groups --NRR' wherein
respectively, (a) R is alkyl and R' is hydrogen or alkyl; (b) R
is aryl and R' is hydrogen or aryl, (c) R is cycloalkyl and R'
35 is hydrogen or alkyl, (d) R is hydrogen and R' is itself linear
aminoalkyl, (e) R is alkyl and R' is itself linear aminoalkyl.

The term aminoalkyl refers to the groups $-(CH_2)_m-NRR'$, wherein m is an integer from 1 to 6, inclusive and $-NRR'$ is alkyl amino, as defined *supra*.

Halo encompasses fluoro, chloro, bromo and iodo.

5 The phrase protecting group, as used herein, means substituents which protect the reactive functional group from undesirable chemical reactions. Examples of such protecting groups include esters of carboxylic acids, ethers of alcohols and acetals and ketals of aldehydes and ketones.

10 The phrase N-protecting group or N-protected as used herein means those groups intended to protect the N-terminus of an amino acid or peptide, to protect an amino group against undesirable reactions during synthetic procedures and includes, but is not limited to, sulfonyl, acetyl, pivaloyl, t-butyloxycarbonyl (Boc),
15 carbonylbenzyloxy (Cbz), benzoyl and an L- or D-aminoacyl residue, which may itself be N-protected similarly. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl, alkoxycarbonyl or an
20 aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a t-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulfuric or
25 phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-charcoal.

30 The phrase COOH-protecting group or carboxyl-protecting group is, an esterifying group, for example an alkyl group (especially methyl or ethyl) or an arylmethyl group (especially benzyl). The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an esterifying group such as an alkyl or
35 aryl methyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an esterifying group

such as an arylmethyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-charcoal using either hydrogen or ammonium formate as a hydrogen source by methods well-known to those skilled in the art.

5 Electrolyte means a solution that has sufficient acid strength to render a basic starting material essentially protonated.

Chemical derivative refers to a subject polypeptide having one or more residues chemically derivatized by reaction of a functional side group. Such derivatized molecules include for
10 example, those molecules in which free amino groups have been derivatized to form amine hydrochlorides, p-toluene sulfonyl groups, carbobenzoxy groups, t-butyloxycarbonyl groups, chloroacetyl groups or formyl groups. Free carboxyl groups may
15 be derivatized to form salts, methyl and ethyl esters or other types of esters or hydrazides. Free hydroxyl groups may be derivatized to form O-acyl or O-alkyl derivatives. The imidazole nitrogen of histidine may be derivatized to form N-imidazolyl-benzylhistidine. Also included as chemical derivatives are those
20 peptides which contain one or more naturally occurring amino acid derivatives of the twenty standard amino acids. For examples, 4-hydroxyproline may be substituted for proline; 5-hydroxylysine may be substituted for lysine; 3-methylhistidine may be substituted for histidine; homoserine may be substituted for
25 serine; and ornithine may be substituted for lysine. Polypeptides of the present invention also include any polypeptide having one or more additions and/or deletions or residues relative to the sequence of a polypeptide whose sequence is shown herein, so long as the requisite activity is maintained.

30 As used herein, fragment means any subject peptide or polypeptide having an amino acid residue sequence shorter than that of a peptide or polypeptide whose full length amino acid residue sequence is shown herein.

A pharmaceutically acceptable salt is one which is prepared
35 by contacting a compound of formulas (I) - (X) according to the specifications therein with an acid whose anion is generally considered suitable for human consumption. Examples of

pharmacologically acceptable acid addition salts include the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, and tartrate salts. All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid with the corresponding compound of structure of Formulas (I) - (X).

Unless otherwise indicated, the preparation methods disclosed herein result in product distributions which include all possible structural isomers. It is understood that physiological response may vary according to stereochemical structure. The isomers may be separated by conventional means such as fractional crystallization or High Pressure Liquid Chromatography (HPLC). Briefly, the absolute configuration of a compound relates to how its substituents are oriented in space about a central atom. This notion becomes significant when coupled with the rigors of chirality. Chirality involves the identity of the substituents about that central atom. Thus, in general, a compound is said to be chiral when four distinctly different groups are bound to a central carbon atom. These groups may be spatially aligned in more than one manner without repeating their individual orientations. That is, a chiral compound may exhibit a mirror image which is also chiral. These mirror images are termed meso configurations, and are each absolute configurations of a chiral compound.

Pharmaceutical compositions according to the present invention comprise one or more peptides and/or peptidomimetics of the invention in association with a pharmaceutically acceptable carrier or excipient, adapted for use in human or veterinary medicine. The compositions may contain from 0.001-99% of the active material. Such compositions may be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers of excipients. The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives. The compositions may optionally further

contain one or more other therapeutic agents which may, if desired, be a chemotherapeutic antiviral agent.

Pharmaceutically acceptable salts of the peptides of this invention may be formed conventionally by reaction with an appropriate acid. The addition salts so formed from addition by acid may be identified by hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, oxalic, methanesulfonic, and the like.

Thus, the peptides and peptidomimetics according to the present invention may be formulated for oral, buccal, parenteral, topical or rectal administration. In particular, these peptides and peptidomimetics may be formulated for injection or for infusion and may be presented in unit dose form in ampoules or in multidose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The present invention further provides a process for preparing a pharmaceutical composition which comprises bringing a peptide and/or peptidomimetic of the invention into association with a pharmaceutically acceptable excipient or carrier.

For administration by injection or infusion, the daily dosage as employed for treatment of an adult human of approximately 70 kg body weight will range from 0.01 mg to 10 mg of each active ingredient, preferably 0.1 to 5 mg, which may be administered in 1 to 4 doses, for example, depending on the route of administration and the condition of the patient. The dosage of the peptide used in the treatment will vary, depending on the seriousness of the disorder, the weight of the patient, the relative efficacy of the peptide and the judgment of the treating physician. However, suitable unit dosages in humans may be between about 0.05 mg to about 100 mg. For example, a unit dosage may be from between about 0.2 mg to about 50 mg. Such a unit dosage, described hereinabove, may be administered more than

once a day, e g., two or three times a day. Thus, the total daily dosage is in the range of about 0.01 mg to 10 mg/kg. Such therapy may extend for several weeks, in an intermittent or uninterrupted manner, until the patient's symptoms are eliminated.

The present invention also provides pharmaceutical compositions which comprise a pharmaceutically effective amount of the one or more peptides and/or peptidomimetics of this invention, or pharmaceutically acceptable salts thereof, and, preferably, a pharmaceutically acceptable carrier or adjuvant. Therapeutic methods of this invention comprise the step of treating patients in a pharmaceutically acceptable manner with those peptides or compositions. Such compositions may be in the form of tablets, capsules, caplets, powders, granules, lozenges, suppositories, reconstitutible powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. The unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional expedients. For example binding agents, such as acacia, gelatin, sorbitol, or polyvinylpyrrolidone; fillers, such as lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants such as magnesium stearate; disintegrants, such as starch, polyvinylpyrrolidone, sodium starch glycolate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulfate.

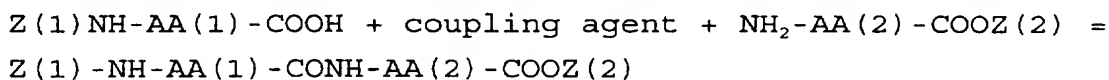
The solid oral compositions may be prepared by conventional methods of blending, filling, tableting, or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art. The tablets may be coated according to methods well-known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may or may not contain conventional additives. For example suspending agents, such as sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel, or hydrogenated edible fats; emulsifying agents, such as sorbitan monooleate or acacia; non-aqueous vehicles (which may include edible oils), such as almond oil, fractionated coconut oil, oily esters selected from the group consisting of glycerine, propylene glycol, ethylene glycol, and ethyl alcohol; preservatives, for instance methyl para-hydroxybenzoate, ethyl para-hydroxybenzoate, n-propyl parahydroxybenzoate, or n-butyl parahydroxybenzoate or sorbic acid; and, if desired, conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms may be prepared by utilizing the peptide and a sterile vehicle, and, depending on the concentration employed, may be either suspended or dissolved in the vehicle. In preparing solutions, the peptides of this invention may be dissolved in water, whereas opiates used heretofore showed only marginal solubility in aqueous media or physiological fluids. Once in solution, the peptide may be injected and filter sterilized before filling a suitable vial or ampoule and subsequently sealing the carrier or storage package. Adjuvants, such as a local anaesthetic, a preservative or a buffering agent, may be dissolved in the vehicle prior to use. Stability of the pharmaceutical composition may be enhanced by freezing the composition after filling the vial and removing the water under vacuum, e.g., freeze drying the composition. Parenteral suspensions may be prepared in substantially the same manner, except that the peptide should be suspended in the vehicle rather than being dissolved. A surfactant or wetting solution may be advantageously included in the composition to facilitate uniform distribution of the peptide.

The stability of the peptides and cyclized peptides of the present invention exceeds that of naturally occurring peptides if substitution is made with D-amino acids in at least 20%, but not more than 50%, of those residues which are naturally present in the (L) configuration. Without being bound by theory, we believe that the increased resistance to enzymatic degradation over of the peptides of the present invention as compared to natural peptides is due to the presence of D-amino acids in the peptides. This switch from L to D amino acids neutralizes the digestion capabilities of many of the ubiquitous peptidases found in the digestive tract. Alternatively, the enhanced stability of the peptides of this invention may also be the result of the introduction of modifications of traditional peptide linkages. For example, the introduction of a cyclizing within the peptide backbone may confer enhanced stability in order to circumvent the effect of many proteolytic enzymes known to digest small peptides in the stomach or other digestive organs and in serum.

The compounds of the present invention are initially synthesized by either solution or by solid phase techniques. Specific exemplary syntheses are described in the examples hereinbelow. The peptides of this invention may be prepared by initially reacting a first appropriately protected amino acid with a second appropriately protected amino acid in an organic solvent inert to the reactants, in the presence of a suitable peptide coupling agent according to the following scheme:



wherein Z(1) is a suitable nitrogen protecting group and Z(2) is a suitable carboxyl protecting group and AA represents any natural or unnatural amino acid residue. The desired peptides may be prepared by utilizing the appropriate amino acids and repeating this reaction sequence as required until a peptide with three to ten amino acid residues has been prepared. A suitable deprotection method is then employed to remove specified or all of the remaining protecting groups or the peptide from the resin.

The first appropriately protected amino acid and, for instance, an appropriately protected tyrosine may be reacted

together in the presence of a suitable peptide coupling agent in a suitably inert organic solvent with stirring, shaking, or agitation to form a protected tyrosine containing dipeptide. Introducing this dipeptide to appropriate protecting group removal conditions affords a selectively deprotected dipeptide which is well-suited for continued peptide synthesis. Contacting this mono-deprotected tyrosine containing dipeptide with an appropriately protected amino acid having a side chain represented as above, in the presence of a suitable peptide coupling agent in a suitably inert organic solvent with stirring, shaking, or agitation forms a protected tyrosine containing tripeptide. This method may be repeated as many times as necessary to achieve the desired peptide.

The method of preparation for peptide synthesis requires specific functional groups to react with other substituents to link amino acid residues in a desired manner to form a peptide possessing a known and desired sequence of amino acid residues. Since amino acids possess at least two reactive functional groups, suitable protection, blocking, or masking of these groups is required to ensure that reaction will occur only at specifically desired sites.

These protecting groups should be introduced to the moiety efficaciously while their removal should be performed under conditions which do not affect other portions of the molecule. In this manner, certain reactions and modifications may be performed on the amino acid, peptide, or other compound, with assurance that the protected functionality will not interfere with the desired reaction. Further, by choosing a protecting group that is sensitive and labile to certain reactive conditions, a reaction scheme may be outlined to advantageously utilize these characteristics to effectively remove the protecting group once the synthesis is complete.

Both N-protecting groups and COOH-protecting groups (see definitions) may be used within the scope of this invention. A variety of protecting groups known in the field of peptide synthesis and recognized by conventional abbreviations therein, may be found in T. Greene, Protective Groups In Organic

Synthesis, Academic Press (1981). Among the preferred protecting groups that may be utilized for suitable protection of reactive nucleophilic substituents include, for example, benzyl (Bz), carbobenzyloxy (Cbz), t-butoxycarbonyl (Boc), or 9-fluorenylmethyloxy-carbonyl (Fmoc).

Coupling of amino acids, which may be the same or different as those described above, to yield small peptides in route to peptides comprised of greater numbers of amino acid residues may be accomplished by employing established techniques in the field of peptide chemistry. A broad range of suitable reactions are described in E. Gross and J. Meinhofer, The Peptides: Analysis, Synthesis, Biology; Modern Techniques of Peptide and Amino Acid Analysis, John Wiley & Sons, (1981) and M. Bodanszky, Principles Of Peptide Synthesis, Springer-Verlag (1984). The peptide coupling agents which may be used to assist condensation of amino and carboxylic acid moieties include N,N'-dicyclohexylcarbodiimide (DCC), N,N'-carbonyl diimidazole (CDI), 1-hydroxy benzotriazole (HOBt), ethyl chloroformate, benzyl chloroformate, 1-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline (EEDQ), benzotriazolyl-oxy-tris-(dimethyl)amino-phosphonium hexafluoro phosphate (BOP) and the like. A preferred technique uses DCC as the coupling reagent. The DCC method may be used with or without catalytic additives such as 4-dimethylaminopyridine (DMAP), copper (II) chloride or HOBt to hasten the reaction and suppress the racemization of the desired compound.

The DCC reaction is often performed at room temperature but may be carried out from about -78 °C to gentle reflux in a variety of solvents that are inert with respect to the reactants. The solvents are normally organic solvents which are polar and aprotic. Preferred solvents include, for example, dichloromethane, chloroform, diethyl ether, tetrahydrofuran (THF), N,N'-dimethylformamide (DMF), and the like. Particularly preferred solvents are dichloromethane and DMF. In general, the coupling reaction may be carried out at atmospheric pressure a temperature of -78 °C to reflux for a period of between 1 and 48 hours. Preferably, the reaction is carried out at about -10° C

to 25° C with stirring, shaking or agitation, over a period of between 4 and 6 hours.

Alternatively, synthesis may be achieved prepared using solid phase synthesis, such as that described by Merrifield, J Am. Chem. Soc., 85, p 2149 (1964), although other equivalent chemical syntheses known in the art can also be used. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected alpha-amino acid to a suitable resin as generally set forth in U.S. Pat. No. 4,244,946.

As an example, Ile protected by BOC is coupled to the a BHA resin using methylene chloride and dimethylformamide. Following the coupling of BOC-Ile to the resin support, the alpha-amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride, TFA alone or with HCl in dioxane. Preferably 50 volume % TFA in methylene chloride is used with 0-5 weight % 1,2 ethanedithiol. The deprotection is carried out at a temperature between about 0° C and room temperature. Other standard cleaving reagents and conditions for removal of specific alpha-amino protecting groups may be used as described in Schroder & Lubke, The Peptides, pp 72-75 (Academic Press 1965).

After removal of the alpha-amino protecting group of Ile, the remaining alpha-amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore. As an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. The selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as coupling reagents are N,N'-dicyclohexyl carbodiimide (DCC) and N,N'-diisopropyl carbodiimide (DICI), or N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder & Lubke, *supra*, in Chapter III and by Kapoor (1970) J. Phar. Sci. 59:127.

Each protected amino acid or amino acid sequence is introduced into the solid phase reactor in about a fourfold excess, and the coupling is carried out in a medium of

dimethylformamide: dichloromethane (1:1) or in DMF or dichloromethane alone. In instances where the coupling is carried out manually, the success of the coupling reaction at each stage of the synthesis is monitored by the ninhydrin reaction, as described by E. Kaiser et al. (1970) Anal. Biochem. 34:595. In cases where incomplete coupling occurs, the coupling procedure is repeated before removal of the alpha-amino protecting group prior to the coupling of the next amino acid. The coupling reactions can be performed automatically, as on a Applied Biosystems automatic synthesizer.

After the desired amino acid sequence has been completed, the intermediate peptide is removed from the resin support by treatment with a reagent, such as liquid hydrogen fluoride, which not only cleaves the peptide from the resin but also cleaves all remaining side chain protecting groups and the alpha-amino protecting group (unless it is an acyl group which is intended to be present in the final peptide) to obtain the peptide. When using hydrogen fluoride for cleaving, anisole or cresol and methylethyl sulfide are included in the reaction vessel as scavengers. When Met is present in the sequence, the BOC protecting group may be cleaved with trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin to eliminate potential S-alkylation.

All patents and publications referred to in the examples, and throughout the specification, are incorporated herein by reference, without admission that such is prior art.

The following nonlimiting examples are provided to illustrate the invention. The skilled artisan will recognize that there may be substitutions and variations of the exemplified methods and compositions which are apparent and can be practiced without departing from the essence of the invention.

EXAMPLES

Example 1. Peptide Synthesis

The synthesis of the peptide of SEQ ID NO:1 (Thr-Ile-Glu-Asp-Ser-Tyr-Arg-Lys-Gln-Val-Val-Ile-Asp) is conducted in a

stepwise manner on a MBHA hydrochloride resin, such as available from Bachem, Inc. (Torrance, CA) having a substitution range of about 0.1 to 0.5 mmoles/gm. resin.

5 All equipment employed in the examples is commercially available. Unless otherwise indicated, all starting materials employed in the examples are commercially available. Sources for these materials include Sigma Chemical Co. (St. Louis, MO), Aldrich Chemical Co. (Milwaukee, WI), Lancaster Synthesis (Windham, NH), Fisher Scientific (Pittsburgh, PA), Boehringer
10 Mannheim Biochemicals (Indianapolis, IN), Fluka Chemical Corp. (Ronkonkoma, NY) and Chemical Dynamics Corp. (South Plainfield, NJ). Most of the starting materials were obtained from Aldrich Chemical Co. (Milwaukee, WI).

15 All solvents used in the peptide preparations described herein, e.g. methylene chloride dichloromethane, 2-propanol, dimethylformamide (DMF), and methanol, were Burdick and Jackson "distilled in glass" grade and used without additional distillation. Trifluoroacetic acid (TFA), diisopropylethylamine (DIPEA), piperidine (PIP), dicyclohexylcarbodiimide (DCC),
20 1-hydroxybenzotriazole (HOBt), and [benzotriazole-1-yl-oxy-tris(dimethyl) phosphonium hexafluorophosphate] (BOP) were purchased from Chemical Dynamics Corp. and were "sequenal" grade purity. 1,2-ethanedithiol (EDT) was purchased from Sigma Chemical Co. and used without further purification. All
25 protected amino acids were of the L-configuration unless otherwise indicated and were obtained from Bachem (Torrance, CA).

The synthesis is performed on an Applied Biosystems peptide synthesizer (Foster City, CA) using a suitable program, preferably as follows:

STEP	REAGENTS AND OPERATIONS	MIX TIMES
1	Dichloromethane-80 ml.	2
2	Methanol(MeOH) wash-30 ml.	2
3	Dichloromethane-80 ml.	3
4	50 percent TFA plus 5 percent 1,2-ethane- dithiol in dichloromethane -70 ml.	2
5	Isopropanol wash-80 ml.	2
6	TEA 12.5 percent in dichloromethane -70 ml.	2
7	MeOH wash-40 ml.	2
8	Dichloromethane wash-80 ml.	3
9	Boc-amino acid (10 mmoles) in 30 ml. of either DMF or dichloromethane, depending upon the solubility of the particular protected amino acid, (1 time) plus DCC (10 mmoles) in dichloromethane (reaction time 20-200 min)	

Note: All wash and mix times three minutes except where noted.

Coupling of BOC-ASP(OBz) results in the substitution of about 0.35 mmol ASP per gram of resin. All solvents that are used are carefully degassed, preferably by sparging with an inert gas, e.g., helium or nitrogen, to insure the absence of oxygen.

After deprotection and neutralization, the peptide chain is built stepwise on the resin. Generally, one to two mmol. of BOC-protected amino acid in methylene chloride is used per gram of resin, plus one equivalent of 2 M DCC in methylene chloride, for two hours. When BOC-Arg(Tos) is being coupled, a mixture of 50% DMF and methylene chloride is used. Bzl is used as the hydroxyl side-chain protecting group for Ser and Thr. p-nitrophenyl ester(ONp) can be used to activate the carboxyl end of Asn or Gln; for example, BOC-Asn(ONp) can be coupled overnight using one equivalent of HOBT in a 50% mixture of DMF and methylene chloride. The amido group of Asn or Gln is protected

by Xan when DCC coupling is used instead of the active ester method. 2-Cl-CBZ is used as the protecting group for the Lys side chain. Tos is used to protect the guanidine group of Arg and the imidazole group of His, and the side-chain carboxyl group of Glu or Asp is protected by OBzl.

To cleave and deprotect the resulting protected peptide-resin, it is treated with 1.5 ml anisole, 0.5 ml of methylethylsulfide and 15 ml liquid hydrogen fluoride (HF) per gram of peptide-resin, first at -20 °C for 20 min and then at 0 °C for 30 min. This reaction must be performed with great care owing to the highly toxic and corrosive nature of hydrogen fluoride. This reaction is performed in a commercially available teflon apparatus (Peninsula Research, Inc., Richmond, CA). After complete elimination of HF under high vacuum using a KOH trap, the resin-peptide is washed alternately with dry diethyl ether and chloroform, and the peptides are then extracted with degassed 2 N aqueous acetic acid and separated from the resin by filtration on a Hirsch funnel.

The peptide is purified by gel permeation followed by preparative HPLC as described in Marki et al. (1981) J. Am. Chem. Soc. 103:3178; Rivier, et al. (1984) J. Chromatography 288:303-328; and Hoeger, et al. (1987) BioChromatography 2:134-142. The chromatographic fractions are carefully monitored by HPLC (see below), and only the fractions showing substantial purity are pooled.

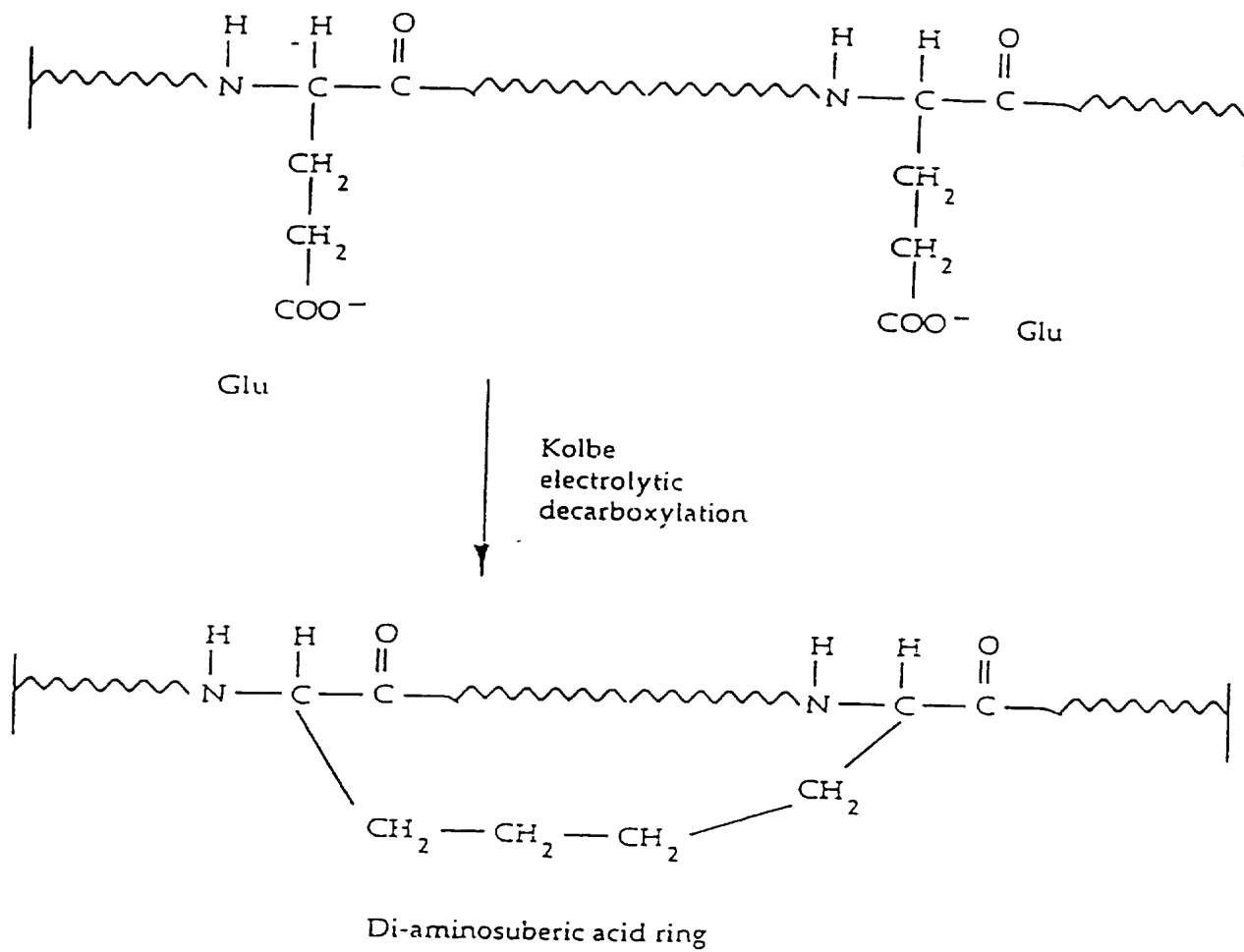
To confirm that the desired sequence is achieved, the peptide is hydrolyzed in sealed evacuated tubes containing constant boiling HCl, 3 μ l of thioglycol/ml and 1 nmol of Nle (as an internal standard) for 9 hours at 140 °C. Amino acid analysis of the hydrolysates using a Beckman 121 amino acid analyzer to determine amino acid ratios allows confirmation that the desired peptide structure has been obtained.

Example 2. Cyclization of Active Peptides

Cyclization "traps" the bioactive conformation of the peptide by making the active conformation part of a ring system

that allows it much less conformational flexibility. In this procedure, aspartate or glutamate residues are introduced into the sequence either in place of non-essential amino acid residues or as added residues in the chain. The new peptide is then
5 subjected to electro-oxidation in which the two residues are decarboxylated, in an intramolecular Kolbe electro-oxidative coupling reaction, resulting in the joining of their respective -CH₂ groups, forming a ring as shown in Fig. 1. This method has been used to make a cyclized β -bend of the dipeptide, Pro-Gly,
10 by placing a glutamic acid residue on the amino and carboxyl ends of this dipeptide and then performing the Kolbe electro-oxidation to form the tetra-(CH₂)-bridge. The Pro-Gly peptide, which has a variety of conformations in solution, when cyclized, was found to adopt the β -bend structure uniquely (Joran, A.,
15 "Conformationally restricted biologically active peptides, methods for their production and uses thereof," U.S. Patent No. 5,364,851.) This method has been used quite recently to synthesize cyclized forms of the peptide vasopressin; these forms have been tested in an *in vitro* adenylate cyclase system and have
20 been found to have prolonged half-lives and greater activity than the native peptide. Therefore, this cyclization procedure may result in enhanced peptide inhibition and in increased half-life. Introduction of the cyclizing rigidifying agent reduces the flexibility of the peptide and concurrently introduces non-polar
25 aliphatic groups into the peptide (such as the tetra-methylene bridge shown in Scheme I) that help promote transport of the peptide through the cell membrane.

Scheme I



Scheme I illustrates an exemplary result of using electrolytic decarboxylation to cyclize peptides to trap them in their active conformations. Either two glutamate, two aspartate, or one glutamate and one aspartate residues are introduced in the chain represented by the wavy line. Under electro-oxidation shown here for two glutamate residues, a tetramethylene bridge forms cyclizing the region of the peptide that is to be held fixed in its bioactive conformation. The two connected residues shown constitute the diamino suberic acid moiety.

It should be noted that, in the synthesis of this new peptide, there are possibly other aspartate and glutamate amino acid residues that can undergo the oxidative decarboxylation. To prevent these reactions from occurring, these Asp and Glu residues are protected as esters during the solid phase synthesis of the peptide. The free Glu residues at positions 44 and 46 are then allowed to undergo the cyclization reaction, after which the protected acid groups are then deprotected.

This cyclization procedure can be performed on other regions of this peptide and on the other two active peptides.

The electrooxidative coupling reaction used to prepare the cyclic peptides of the invention can be performed in a divided or an undivided cell such as a standard glass H-cell, as described in Organic Electrochemistry (2nd Ed.), M. Baizer and H. Lund, eds., Marcel Dekker, New York, 1983, Chap. 5, p 168. For large scale runs, the reaction can be carried out in a plate and frame flow cell as described in Technique of Electroorganic Synthesis, Part III, N. Weinberg and B. Tilak, ed., John Wiley & Sons, New York, 1982, Chap. III, p 179.

Cathode materials useful for the preparation of the compounds of the invention include, but are not limited to, high hydrogen overvoltage materials such as mercury, lead or cadmium. Anode materials include, but are not limited to, materials such as mercury, lead, graphite, or graphite paste, which are stable under electrolysis conditions.

The electrooxidative coupling can occur in aqueous, or aqueous organic electrolytes, comprising solutions of Bronsted acids, such as sulfuric, fluoroboric, and trifluoroacetic acids. Any electrolyte may be selected that has sufficient acid strength to render a basic starting material protonated. A dilute solution of trifluoroacetic acid is most preferred.

Although the preferred method of electrolysis to obtain the compounds of this invention takes place under constant current conditions, the oxidative coupling could also be performed using controlled potential electrolysis, as understood by those skilled in the art. Typical current densities are between 1 and 5000 milliamps(mA)/cm², preferably between 10 and 100 mA/cm². The reaction is preferably carried out at a temperature in the range of about 0 °C to 37 °C, more preferably about 10 °C.

A standard glass H-cell (200 ml volume, glass frit separator) was equipped with a mercury pool cathode (12 cm² area), a magnetic stirrer, and a platinum foil anode. The cell reservoir was filled with 40 mM trifluoroacetic acid (110 ml) and placed in a water bath maintained at 10 °C. The catholyte was purged with nitrogen. The starting peptide (20 mg) was added to the catholyte and constant current electrolysis was initiated at 0.1 A. The reaction progress was followed by HPLC and after passage of 1,060 coulombs, all the substrate had been consumed and the electrolysis was terminated. The catholyte was recovered and adjusted to pH 8 with NaOH. The pH-adjusted catholyte was extracted with chloroform (2 times 70 ml). The extract was freeze dried and the resultant powdery material extracted with acetonitrile (HPLC grade). This was filtered through a sintered-glass filter (fine porosity) and was reduced in volume on a rotary evaporator using a mechanical vacuum pump to a volume of 2 ml. This material was purified by reversed-phase high pressure liquid chromatography using a Waters HPLC system with a 0.46 x 0.25 cm column packed with 5 µm C₁₈ silica, 300 Å pore size. Buffer A is an aqueous 0.1% (vol/vol) trifluoroacetic acid solution (1.0 ml of TFA per 1000 ml solution); Buffer B is 100% acetonitrile. The determination is run at room temperature with a gradient from 15.5% Buffer B to 75% Buffer B over a 30 min.

The flow rate is 2.2 ml per minute, and the retention time is 25.0 min.

The structure was confirmed by 300 MHz ^1H NMR, ^{13}C NMR, and electrospray mass spectroscopy.

5 The amounts of the reactants and the conditions required to facilitate reaction and encourage efficient completion of the aforementioned Examples may vary widely. However, in general, the amounts of material employed to induce reaction in the processes discussed above will be substantially stoichiometric, 10 unless otherwise specified. In the following examples, reaction concentrations are generally held at 0.1 M for the reactants, unless a higher concentration or dilution would be particularly useful for influencing the direction of a specific reaction. In practice, the amounts used will depend upon variations in 15 reaction conditions and the nature of the reactants as readily apparent to one of ordinary skill in the art.

In any of the methods described hereinabove, the desired products may be isolated from the reaction mixture by crystallization. Alternatively, chromatographic techniques 20 including, but not limited to, normal phase, reverse phase, ion-exchange, affinity, or gel permeation, may be employed, as well as electrophoresis or extraction or other means.

Example 3. Oocyte Maturation Assay

25 Using the method described in Chung et al. (1991) Anticancer Res. 11:1373-1378, test peptides, cyclized peptides and/or peptidomimetics are injected into immature oocytes at various doses. The oocytes are co-injected with recombinant transforming ras p21 obtained from the National Cancer Institute of Japan. Alternatively, the oncogenic ras p21 can be prepared by the 30 ordinary skilled artisan without the expense of undue experimentation as described in Chung et al. (1991) supra and in Chung et al. (1992) *Exp. Cell. Res.* 203:329-335. The maturation of the oocytes is evaluated microscopically at low power (20 X), using a Nikon Diaphot microscope, for example. Percent 35 inhibition is calculated based on comparisons with oocytes which are injected with 0.05 mg/ml oncogenic ras p21.

The following results were obtained using a dose of each peptide equivalent to an internal oocyte concentration of 50 nM:

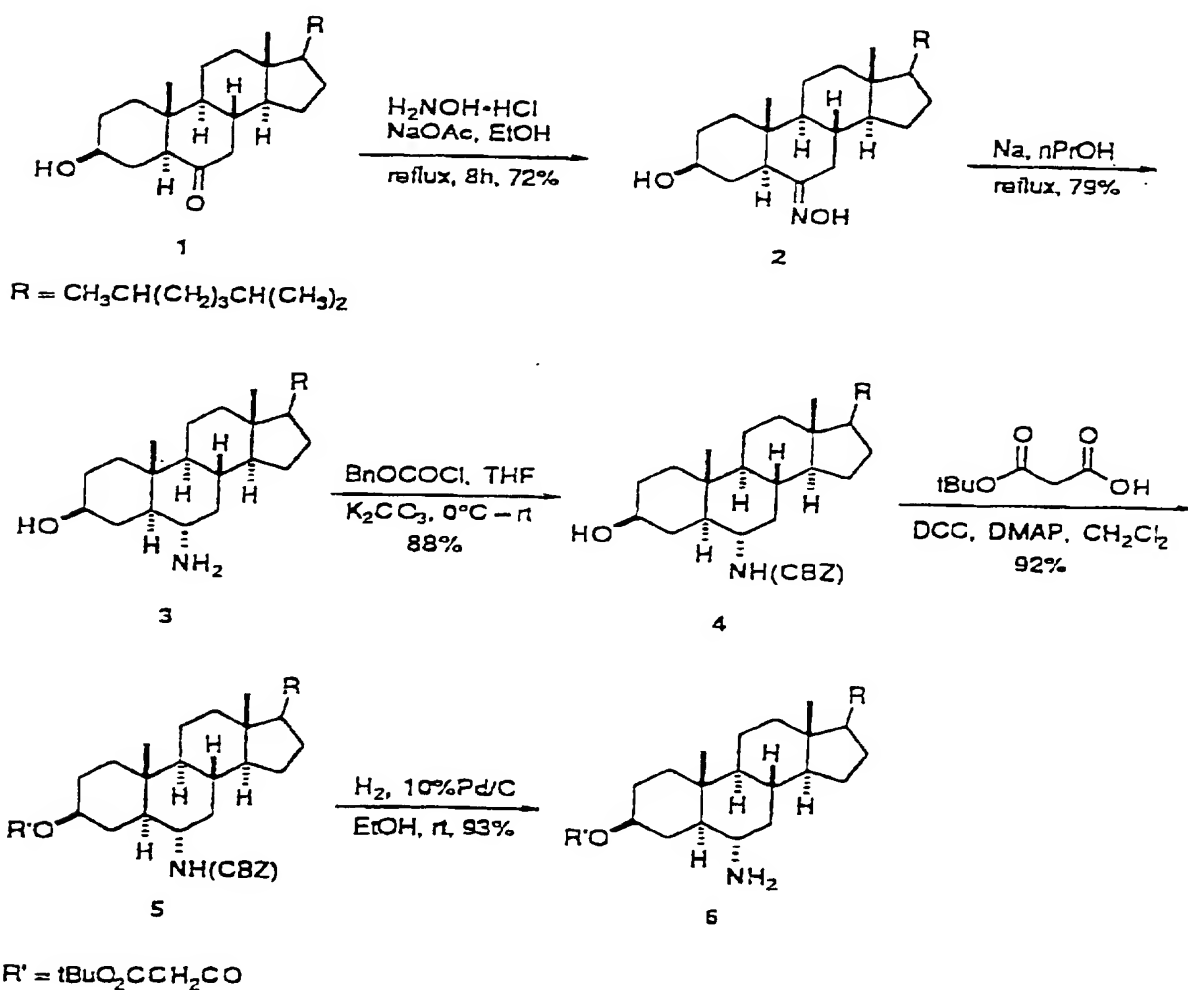
Peptide	OR	Sequence ID Number	Percent Inhibition of <u>ras</u> -Induced Maturation
		6	28
Val-Val-Ile			34
		7	56
Lys-Arg-Val			22
		7	76
		8	92
		2	38
		9	65
		4	22

The peptidomimetics and cyclic peptides of the present invention will be similarly effective in inhibiting oocyte maturation in response to the oncogenic ras p21 protein, and in inhibiting oncogenesis.

Example 4. Synthesis of Peptidomimetic p21 ras Inhibitor

A representative peptidomimetic of the present invention is synthesized according to Scheme II, as further described hereinbelow.

5 Scheme II



Steroid 1 was commercially available, and used without further purification. Mono-t-butylmalonate was prepared by literature methods [Brunwin, D.M.; et al. (1971) *J. Chem. Soc. C.* 3756]. THF was distilled from sodium/benzophenone under Ar. Methylene chloride and ethanol (absolute) were distilled from CaH₂ under Ar. Benzylchloroformate and n-propyl alcohol are commercially

available, and used without further purification or drying. All reactions performed under an atmosphere of Ar unless otherwise noted.

5- α -3- β -hydroxy-6-oximinocholestane (2): Cholestanone 1 (1.00 g, 2.5 mmol), NaOAc (352 mg, 4.3 mmol) and hydroxylamine hydrochloride (197 mg, 2.8 mmol) were heated at reflux in absolute ethanol (15 ml). The reaction was efficiently stirred under Ar for 11h at reflux. The reaction was cooled, and the solvent removed on the rotary evaporator. The resulting white solid was dissolved in CHCl_3 , and washed once with brine (80 ml). The organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The yield of crude material was 1.068 g of a lightly colored solid. The material was recrystallized from absolute ethanol (15.5 mL) to give 752 mg (72%) of white needles, mp = 202-204°C (dec). ^1H NMR(CDCl_3): δ 3.60 (m, 1H), 3.33 (dd, J = 4.37, 13.6 Hz, 1H), 2.10-1.75 (broad m, 6H), 1.70-1.45 (broad m, 5H), 1.42-1.28 (broad m, 8H), 1.14 (m, 9H), 0.92 (d, J = 6.87 Hz, 3H), 0.88 (d, J = 6.54 Hz, 6H), 0.77 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (CDCl_3): δ 159.55, 70.77, 56.39, 55.91, 54.04, 49.26, 42.60, 39.42, 39.20, 38.57, 35.92, 35.84, 35.63, 35.43, 31.24, 30.40, 29.39, 27.87, 27.70, 23.80, 23.53, 22.51, 22.26, 21.17, 18.36, 12.34, 11.79, IR (neat film): 3354, 2941, 1667, 1467, 1065, 978 cm^{-1} .

5- α -6- α -amino-3- β -hydroxycholestane (3): Oxime 2 (752 mg, 1.8 mmol) was dissolved with good stirring in boiling n-propyl alcohol (32 mL). The flask was removed from the oil bath, and small pieces of freshly prepared sodium wire (2.898 g, 126 mmol) were added at a rate sufficient to maintain the reflux. After the addition of the sodium was complete, the flask was lowered into the bath, and stirred at reflux for 2h (a thick, white crust forms). The reaction was cooled to room temperature, and carefully quenched by slow, dropwise addition of water under an inert atmosphere. The quenched reaction was extracted twice with CHCl_3 (50 mL), and the extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The yield of a vanilla colored solid was 723 mg. The material was purified by flash chromatography on silica in $\text{CHCl}_3/\text{MeOH}$ (3:2) to give 577 mg

(79%) of a vanilla colored solid. Alternatively, the product can be recrystallized from EtOAc. ^1H NMR (CDCl_3): δ 3.59 (m, 1H), 2.60 (dd, $J = 2.87, 10.35, 20.73\text{Hz}$, 1H), 2.09 (d, $J = 11.79\text{Hz}$, 1H), 1.99 (d, $J = 12.94\text{Hz}$, 1H), 1.85 (m, 3H), 1.78 - 1.45 (broad m, 10H), 1.36 (m, 5H), 1.24 - 0.96 (m, 9H), 0.89 (m, 10H), 0.83 (s, 3H), 0.77 (m, 2H), 0.67 (s, 3H).

***N*-(benzyloxy carbonyl)-5- α -6- α -amino-3- β -hydroxycholestane (4):**

The amine 3 (465 mg, 1.15 mmol) and anhydrous K_2CO_3 (457 mg, 3.3 mmol) were stirred in dry THF (4 mL), and cooled to 0°C in an ice-water bath. Benzyl-chloroformate (0.16 mL, 1.15 mmol) was added dropwise, and the reaction was stirred at 0°C for 15 min, then at room temperature for 6h. The reaction was diluted with water and poured into saturated NaHCO_3 (15 mL). A thick, flocculent white precipitate formed. The aqueous mixture was extracted with CHCl_3 (20 mL), and the aqueous layer was saturated with NaCl and extracted with CHCl_3 (5x20 mL). The organic extracts were washed with brine (40 mL), dried over Na_2SO_4 , filtered, and concentrated. The yield of crude material was 649 mg of a tan solid. The material was flash chromatographed on silica in Hex/EtOAc (1:1), (using a little CHCl_3 to help dissolve material) to give 546 mg (88%) of a white solid. ^1H NMR (CDCl_3): δ 7.88 (m, 4H), 7.23 (s, 1H), 5.08 (d, $J = 3.08\text{Hz}$, 2H), 4.86 (d, $J = 9.46\text{Hz}$, 1H), 3.53 (m, 1H), 3.50 (s, 1H; overlaps with the multiplet at 3.53), 2.00 (d, $J = 12.35\text{Hz}$, 2H), 1.85 (m, 3H), 1.53 (m, 4H), 1.49 - 1.22 (broad m, 9H), 1.20 - 0.98 (broad m, 10H), 0.90 (m, 9H), 0.87 (s, 3H), 0.77 (m, 2H), 0.66 (s, 3H). IR (neat film): 3346 (broad), 1691, 1544, 1022 cm^{-1} .

***N*-(benzyloxy carbonyl)-5- α -6- α -amino-3- β -mono-*t*-butyl malonyl cholestane (5):**

The amine 4 (144.4 mg, 0.27 mmol), mono-*t*-butyl malonate (107.7 mg, 0.67 mmol), and DMAP were dissolved in dry CH_2Cl_2 (1.2 mL), and stirred efficiently at room temperature. DCC (67.4 mg, 0.33 mmol) was added in one portion under a stream of Ar. The reaction was stirred at room temperature for 23h, then diluted with ether, and filtered through a pad of Celite (a white solid remains on the pad). The filtrate was washed with 10% citric acid (20 mL), saturated NaHCO_3 (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4 , filtered and

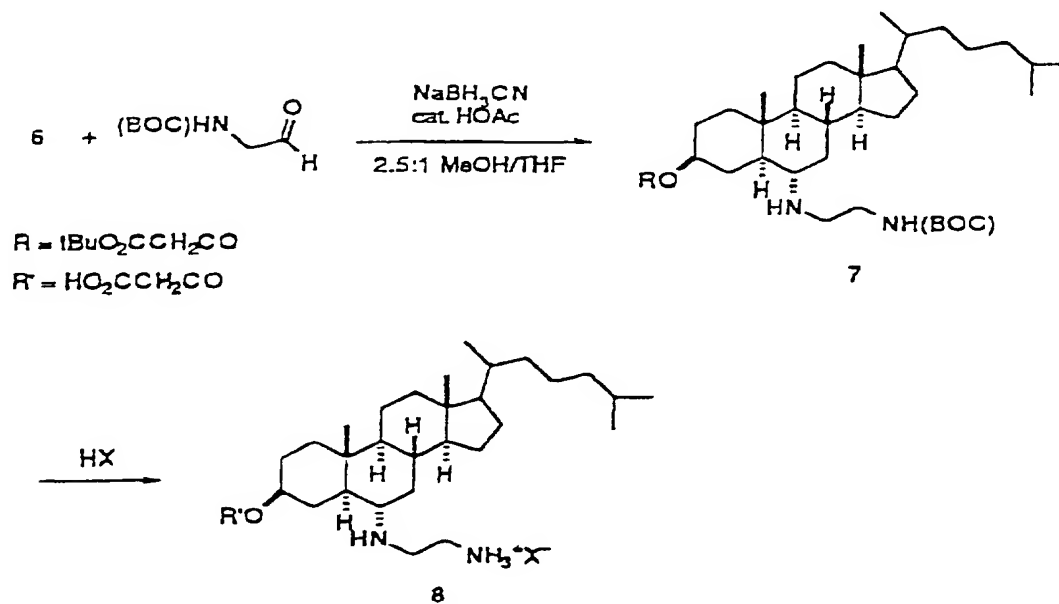
concentrated. The yield of crude material was 200 mg. The material was flash chromatographed in Hex/EtOAc (6.7:1) to give 168.7 mg (92%) of a yellow-gold residue ^1H NMR (CDCl_3): δ 7.36 (s, 4H), 7.29 (s, 1H), 5.08 (q, $J = 12.25, 27.09\text{Hz}$, 2H), 4.70 (m, 1H), 4.38 (d, $J = 9.56\text{Hz}$, 1H), 3.27 (s, 2H), 2.00 (m, 2H), 1.85 (m, 4H), 1.54 (m, 3H), 1.48 (s, 9H), 1.35 (m, 8H), 1.11 (m, 11H), 0.89 (m, 12H), 0.75 (m, 2H), 0.66 (s, 3H).

The N-CBZ group of 5 was cleanly removed by hydrogenolysis using 10% palladium on carbon under a hydrogen atmosphere to give 6 in 93% yield. Trials employing 1,4-cyclohexadiene as the hydrogen source [Felix et al. (1978) *J. Org. Chem.* **43**:4194] produced 6 in only 23% yield, even when a large excess of the diene was used. Longer reaction time did not improve the yield. **5- α -6- α -amino-3- β -mono-*t*-butyl malonyl cholestane (6)**: 5 (200.7 mg, 0.3 mmol) and 10% palladium on carbon (194 mg) were stirred vigorously in abs. EtOH (1.8 mL). The system was flushed with a balloon of hydrogen, and an atmosphere of hydrogen was maintained by 2 balloons of hydrogen. The reaction was stirred for 20h at room temperature, then vented with Ar, and suction-filtered through a tightly packed pad of Celite. The flask and filter cake were thoroughly washed with 1:1 EtOH/THF. The filtrate was concentrated in vacuo to give 167.8 mg of material. The crude product was flash chromatographed first in Hex/EtOAc (3:2) to elute off minor byproducts, then $\text{CHCl}_3/\text{MeOH}$ (9:1) to give the product in a yield of 152.3 mg (93%) of a golden residue. ^1H NMR (CDCl_3): δ 4.76 (m, 1H), 3.27 (s, 2H), 2.60 (m, 1H), 2.22 (m, 1H), 2.05 - 1.71 (broad m, 6H), 1.51 (s, 3H), 1.49 (s, 9H), 1.34 (broad m, 8H), 1.24 - 0.97 (broad m, 12H), 0.92 (d, $J = 6.55\text{Hz}$, 3H), 0.88 (d, $J = 6.64\text{Hz}$, 6H), 0.85 (s, 3H), 0.75 (m, 2H), 0.67 (s, 3H), IR (neat film): 3368, 2946, 2868, 1747, 1729, 1144, 1008 cm^{-1} .

Reductive amination of N(BOC) aminoacetaldehyde [Buchardt et al. (1993) *Org. Prep. Proc. Int.* **25**:457] is promoted by the use of NaBH_3CN and catalytic acetic acid. *t*-Butylester and BOC groups are removed. The general plan is given in Scheme III.

51

Scheme III



SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: INNAPHARMA, INC.
- (ii) TITLE OF INVENTION: Peptides and Peptidomimetics Inhibiting the Oncogenic Action of P21 Ras
- (iii) NUMBER OF SEQUENCES: 52
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Greenlee, Winner and Sullivan, P.C.
 - (B) STREET: 5370 Manhattan Circle, Suite 201
 - (C) CITY: Boulder
 - (D) STATE: Colorado
 - (E) COUNTRY: US
 - (F) ZIP: 80303
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER: PCT/US96/15098
 - (B) FILING DATE: 20-SEP-1996
 - (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: US 08/531,525
 - (B) FILING DATE: 21-SEP-1995
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: US 60/004,091
 - (B) FILING DATE: 21-SEP-1995
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Ferber, Donna M.
 - (B) REGISTRATION NUMBER: 33,878
 - (C) REFERENCE/DOCKET NUMBER: 37-94A WO
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: (303) 499-8080
 - (B) TELEFAX: (303) 499-8089

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 6 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Ile Lys Arg Val Lys Asp
1 5

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys Cys Asp Leu Ala
1 5

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: -
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Cys Asp Leu Ala Ala Arg Thr
1 5

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Asp Leu Ala Ala
1

(2) INFORMATION FOR SEQ ID NO:5:

54

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 188 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met	Thr	Glu	Tyr	Lys	Leu	Val	Val	Val	Gly	Ala	Gly	Gly	Val	Gly	Lys	1	5	10	15
Ser	Ala	Leu	Thr	Ile	Gln	Leu	Ile	Gln	Asn	His	Phe	Val	Asp	Glu	Tyr	20	25	30	
Asp	Pro	Thr	Ile	Glu	Asp	Ser	Tyr	Arg	Lys	Gln	Val	Val	Ile	Asp	Gly	35	40	45	
Glu	Thr	Cys	Leu	Leu	Asp	Ile	Leu	Asp	Thr	Ala	Gly	Gln	Glu	Glu	Tyr	50	55	60	
Ser	Ala	Met	Arg	Asp	Gln	Tyr	Met	Arg	Thr	Gly	Glu	Gly	Phe	Leu	Cys	65	70	75	80
Val	Phe	Ala	Ile	Asn	Asn	Thr	Lys	Ser	Phe	Glu	Asp	Ile	His	Gln	Tyr	85	90	95	
Arg	Glu	Gln	Ile	Lys	Arg	Val	Lys	Asp	Ser	Asp	Asp	Val	Pro	Met	Val	100	105	110	
Leu	Val	Gly	Asn	Lys	Cys	Asp	Leu	Ala	Ala	Thr	Val	Glu	Ser	Arg	Gln	115	120	125	
Ala	Gln	Asp	Leu	Ala	Arg	Ser	Tyr	Gly	Ile	Pro	Tyr	Ile	Glu	Thr	Ser	130	135	140	
Ala	Lys	Thr	Arg	Gln	Gly	Val	Glu	Asp	Ala	Phe	Tyr	Thr	Leu	Val	Arg	145	150	155	160
Glu	Ile	Arg	Gln	His	Lys	Leu	Arg	Lys	Leu	Asn	Pro	Pro	Asp	Glu	Ser	165	170	175	
Gly	Pro	Gly	Cys	Met	Ser	Cys	Lys	Cys	Val	Leu	Ser					180	185		

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 13 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 15 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(iii) HYPOTHETICAL: NO

Tyr Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro
1 5 10 15

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(iii) HYPOTHETICAL: NO

Gly Asn Lys Cys Asp Leu Ala Ala Arg Thr Val Glu
1 5 10

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(iii) HYPOTHETICAL: NO

Cys Asp Leu Ala Ala Arg Thr
1 5

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 215 amino acids

56

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Arabidopsis thaliana*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met	Ala	Ala	Pro	Pro	Ala	Arg	Ala	Arg	Ala	Asp	Tyr	Asp	Tyr	Leu	Ile	1	5	10	15
Lys	Leu	Leu	Leu	Ile	Gly	Asp	Ser	Gly	Val	Gly	Lys	Ser	Cys	Leu	Leu	20	25	30	
Leu	Arg	Phe	Ser	Asp	Gly	Ser	Phe	Thr	Thr	Ser	Phe	Ile	Thr	Thr	Ile	35	40	45	
Gly	Ile	Asp	Phe	Lys	Ile	Arg	Thr	Ile	Glu	Leu	Asp	Gly	Lys	Arg	Ile	50	55	60	
Lys	Leu	Gln	Ile	Trp	Asp	Thr	Ala	Gly	Gln	Glu	Arg	Arg	Thr	Ile	Thr	65	70	75	80
Thr	Ala	Tyr	Tyr	Arg	Gly	Ala	Met	Gly	Ile	Leu	Leu	Val	Tyr	Asp	Val	85	90	95	
Thr	Asp	Glu	Ser	Ser	Phe	Asn	Asn	Ile	Arg	Asn	Trp	Ile	Arg	Asn	Ile	100	105	110	
Glu	Gln	His	Ala	Ser	Asp	Asn	Val	Asn	Lys	Ile	Leu	Val	Gly	Asn	Lys	115	120	125	
Ala	Asp	Met	Asp	Glu	Ser	Lys	Arg	Ala	Val	Pro	Thr	Ala	Lys	Gly	Gln	130	135	140	
Ala	Leu	Ala	Asp	Glu	Tyr	Gly	Ile	Lys	Phe	Phe	Glu	Thr	Ser	Ala	Lys	145	150	155	160
Thr	Asn	Leu	Asn	Val	Glu	Glu	Val	Phe	Phe	Ser	Ile	Gly	Arg	Asp	Ile	165	170	175	
Lys	Gln	Arg	Leu	Ser	Asp	Thr	Asp	Ser	Arg	Ala	Glu	Pro	Ala	Thr	Ile	180	185	190	
Lys	Ile	Ser	Gln	Thr	Asp	Gln	Ala	Ala	Gly	Ala	Gly	Gln	Ala	Thr	Gln	195	200	205	
Lys	Ser	Ala	Cys	Cys	Gly	Thr										210	215		

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Arabidopsis thaliana*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```

Met Ala Gly Tyr Ala Asp Glu Glu Tyr Asp Tyr Leu Phe Lys Leu Val
 1           5           10           15
Leu Ile Gly Asp Ser Gly Val Gly Lys Ser Asn Leu Leu Ser Arg Phe
          20           25           30
Thr Lys Asn Phe Asn Leu Glu Ser Lys Ser Thr Ile Gly Val Glu Phe
          35           40           45
Ala Thr Lys Thr Thr Lys Val Glu Gly Lys Val Val Lys Ala Gln Ile
          50           55           60
Trp Asp Thr Ala Gly Gln Glu Arg Tyr Arg Ala Ile Thr Ser Ala Tyr
65           70           75           80
Tyr Arg Gly Ala Val Gly Ala Leu Leu Ile Tyr Asp Val Thr Arg His
          85           90           95
Ala Thr Phe Glu Asn Ala Ala Arg Trp Leu Arg Glu Leu Arg Gly His
          100          105          110
Thr Asp Pro Asn Ile Val Val Met Leu Ile Gly Asn Lys Cys Asp Leu
          115          120          125
Arg His Leu Val Ala Val Lys Thr Glu Glu Ala Lys Ala Phe Ala Glu
          130          135          140
Arg Glu Ser Leu Tyr Phe Met Glu Thr Ser Ala Leu Asp Ala Thr Asn
145          150          155          160
Val Glu Asn Ala Phe Thr Glu Val Leu Thr Gln Ile His Lys Ile Val
          165          170          175
Ser Lys Arg Ser Val Asp Gly Gly Gly Ser Ala Asp Leu Pro Gly Lys
          180          185          190
Gly Glu Thr Ile Asn Val Lys Glu Asp Gly Ser Val Leu Lys Arg Met
          195          200          205
Gly Cys Cys Ser Asn
          210

```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Arabidopsis thaliana*

58

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```

Met Ser Ser Asp Asp Glu Gly Arg Glu Glu Tyr Phe Lys Ile Val Val
1          5          10          15
Ile Gly Asp Ser Ala Val Gly Lys Ser Asn Leu Leu Ser Arg Tyr Ala
20          25          30
Arg Asn Glu Phe Ser Ala Asn Ser Lys Ala Thr Ile Gly Val Glu Phe
35          40          45
Gln Thr Gln Ser Met Ile Glu Gly Lys Glu Val Lys Ala Gln Ile Trp
50          55          60
Asp Thr Ala Gly Gln Glu Phe Arg Ala Val Thr Ser Tyr Tyr Arg Gly
65          70          75          80
Ala Val Gly Ala Leu Val Val Tyr Asp Ile Thr Arg Arg Thr Thr Phe
85          90          95
Glu Ser Val Gly Arg Trp Leu Asp Glu Leu Lys Ile His Ser Asp Thr
100         105         110
Thr Val Ala Arg Met Leu Val Gly Asn Lys Cys Asp Leu Glu Asn Ile
115         120         125
Arg Ala Val Ser Val Glu Glu Gly Lys Ala Leu Ala Glu Glu Glu Gly
130         135         140
Leu Phe Phe Val Glu Thr Ser Ala Leu Asp Ser Thr Asn Val Lys Thr
145         150         155         160
Ala Phe Glu Met Val Ile Leu Asp Ile Tyr Asn Asn Val Ser Arg Lys
165         170         175
Gln Leu Asn Ser Asp Thr Tyr Lys Asp Glu Leu Thr Val Arg Val Ser
180         185         190
Leu Val Lys Asp Asp Asn Ser Ala Ser Lys Gln Ser Ser Gly Phe Ser
195         200         205
Cys Cys Ser Ser Thr
210

```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 201 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Discopyge ommata*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```

Met Asn Pro Glu Tyr Asp Tyr Leu Phe Lys Leu Leu Leu Ile Gly Asp
1          5          10          15
Ser Gly Val Gly Lys Ser Cys Leu Leu Leu Arg Phe Ala Asp Asp Thr

```

59

	20		25		30	
Tyr Thr Glu Ser Tyr Ile Ser Thr Ile Gly Val Asp Phe Lys Ile Arg	35	40	45			
Thr Ile Glu Leu Asp Gly Lys Thr Ile Lys Leu Gln Ile Trp Asp Thr	50	55	60			
Ala Gly Gln Glu Arg Phe Arg Thr Ile Thr Ser Ser Tyr Tyr Arg Gly	65	70	75	80		
Ala His Gly Ile Ile Val Val Tyr Asp Val Thr Asp Gln Glu Ser Phe	85	90	95			
Asn Asn Val Lys Gln Trp Leu Gln Glu Ile Asp Arg Tyr Ala Ser Glu	100	105	110			
Asn Val Asn Lys Leu Leu Val Gly Asn Lys Cys Asp Leu Thr Thr Lys	115	120	125			
Lys Val Val Asp Tyr Thr Thr Lys Glu Phe Ala Asp Ser Leu Gly Ile	130	135	140			
Pro Phe Leu Glu Thr Ser Ala Lys Asn Ala Thr Asn Val Glu Gln Ala	145	150	155	160		
Phe Met Thr Met Ala Ala Glu Ile Lys Lys Arg Met Gly Pro Gly Ala	165	170	175			
Thr Ser Gly Gly Ser Glu Lys Ser Asn Val Asn Ile Gln Ser Thr Pro	180	185	190			
Val Lys Ser Ser Gly Gly Gly Cys Cys	195	200				

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 202 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Lymnea stagnalis*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ser Thr Met Asn Pro Asp Tyr Asp Tyr Leu Phe Lys Leu Leu Leu	1	5	10	15
Ile Gly Asp Ser Gly Val Gly Lys Ser Cys Leu Leu Leu Arg Phe Ala	20	25	30	
Asp Asp Thr Tyr Thr Glu Ser Tyr Ile Ser Thr Ile Gly Val Asp Phe	35	40	45	
Lys Ile Arg Thr Ile Glu Leu Asp Gly Lys Thr Ile Lys Leu Gln Ile	50	55	60	
Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Thr Ile Thr Ser Ser Tyr				

60

65					70					75				80	
Tyr	Arg	Gly	Ala	His	Gly	Ile	Ile	Val	Val	Tyr	Asp	Val	Thr	Asp	Gln
				85					90					95	
Glu	Ser	Phe	Asn	Asn	Val	Lys	Gln	Trp	Leu	Gln	Glu	Ile	Asp	Arg	Tyr
			100					105					110		
Ala	Ser	Glu	Asn	Val	Asn	Lys	Leu	Leu	Val	Gly	Asn	Lys	Ser	Asp	Leu
			115				120					125			
Thr	Thr	Lys	Lys	Val	Asp	Phe	Thr	Thr	Ala	Lys	Glu	Tyr	Ala	Asp	Gln
	130					135					140				
Leu	Gly	Ile	Pro	Phe	Leu	Glu	Thr	Ser	Ala	Lys	Asn	Ala	Thr	Asn	Val
145					150					155					160
Glu	Gln	Ala	Phe	Met	Thr	Met	Ala	Ala	Glu	Ile	Lys	Asn	Arg	Met	Gly
				165					170					175	
Pro	Ile	Thr	Ala	Ser	Asp	Ser	Lys	Pro	Ser	Val	Lys	Ile	Asn	Ser	Ser
			180					185					190		
Thr	Pro	Ser	Ala	Asn	Lys	Gly	Gly	Cys	Cys						
		195				200									

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 208 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

- (vi) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met	Ala	Tyr	Ala	Tyr	Leu	Phe	Lys	Tyr	Ile	Ile	Ile	Gly	Asp	Thr	Gly
1				5					10					15	
Val	Gly	Lys	Ser	Cys	Leu	Leu	Leu	Gln	Phe	Thr	Asp	Lys	Arg	Phe	Gln
			20					25					30		
Pro	Val	His	Asp	Leu	Thr	Ile	Gly	Val	Glu	Phe	Gly	Ala	Arg	Met	Ile
		35					40					45			
Thr	Ile	Asp	Gly	Lys	Gln	Ile	Lys	Leu	Gln	Ile	Trp	Asp	Thr	Ala	Gly
	50				55						60				
Gln	Glu	Ser	Phe	Arg	Ser	Ile	Thr	Arg	Ser	Tyr	Tyr	Arg	Gly	Ala	Ala
65				70						75					80
Gly	Ala	Leu	Leu	Val	Tyr	Asp	Ile	Thr	Arg	Arg	Asp	Thr	Phe	Asn	His
				85					90					95	
Leu	Thr	Thr	Trp	Leu	Glu	Asp	Ala	Arg	Gln	His	Ser	Asn	Ser	Asn	Met
			100					105					110		
Val	Ile	Met	Leu	Ile	Gly	Asn	Lys	Ser	Asp	Leu	Glu	Arg	Arg	Glu	Val

61

115	120	125																	
Lys	Lys	Glu	Glu	Gly	Glu	Ala	Phe	Ala	Glu	His	Gly	Leu	Ile	Phe	Met				
	130					135					140								
Glu	Thr	Ala	Lys	Thr	Ala	Ser	Val	Glu	Glu	Ala	Phe	Ile	Asn	Thr	Ala				
145					150					155					160				
Lys	Glu	Ile	Tyr	Glu	Lys	Ile	Gln	Glu	Gly	Val	Phe	Asp	Ile	Asn	Asn				
				165					170					175					
Glu	Ala	Asn	Gly	Ile	Lys	Ile	Gly	Pro	Gln	His	Ala	Ala	Thr	Asn	Ala				
			180					185					190						
Thr	His	Ala	Gly	Asn	Gln	Gly	Gly	Gln	Gln	Ala	Gly	Gly	Gly	Cys	Cys				
		195				200						205							

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 210 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Lymnea stagnalis*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met	Ser	Tyr	Ala	Tyr	Leu	Phe	Lys	Tyr	Ile	Ile	Ile	Gly	Asp	Thr	Gly				
1				5					10					15					
Val	Gly	Lys	Ser	Cys	Leu	Leu	Leu	Gln	Phe	Thr	Asp	Lys	Arg	Phe	Gln				
			20					25					30						
Pro	Val	His	Asp	Leu	Thr	Ile	Gly	Val	Glu	Phe	Gly	Ala	Arg	Met	Ile				
		35					40					45							
Thr	Ile	Asp	Gly	Lys	Gln	Ile	Lys	Leu	Gln	Ile	Trp	Asp	Thr	Ala	Gly				
	50					55					60								
Gln	Glu	Ser	Phe	Arg	Ser	Ile	Thr	Arg	Ser	Tyr	Tyr	Arg	Gly	Ala	Ala				
65					70					75					80				
Gly	Ala	Leu	Leu	Val	Tyr	Asp	Ile	Thr	Arg	Arg	Asp	Thr	Phe	Asn	His				
				85					90					95					
Leu	Thr	Thr	Trp	Leu	Glu	Asp	Ala	Arg	Gln	His	Ser	Asn	Ser	Asn	Met				
			100					105					110						
Val	Ile	Met	Leu	Ile	Gly	Asn	Lys	Ser	Asp	Leu	Glu	Ala	Arg	Arg	Val				
	115						120					125							
Lys	Lys	Glu	Glu	Gly	Glu	Ala	Phe	Arg	Glu	His	Gly	Leu	Ile	Phe	Met				
	130					135					140								
Glu	Thr	Ser	Ala	Lys	Thr	Ala	Ala	Asn	Val	Glu	Glu	Ala	Phe	Ile	Asn				
145					150					155					160				

62

Thr Ala Lys Glu Ile Tyr Gln Lys Ile Gln Asp Gly Val Phe Asp Ile
 165 170 175

Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ser Pro Ala
 180 185 190

Ser Gln Ser Leu Asn Val Gly Gly Ser Gly Gly Asn Gln Gly Gly Asn
 195 200 205

Cys Cys
 210

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 208 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Oryctolagus cuniculus*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
 1 5 10 15

Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
 20 25 30

Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
 35 40 45

Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gln
 50 55 60

Glu Ser Phe Arg Ser Ile Arg Ser Tyr Tyr Arg Gly Ala Gly Ala Leu
 65 70 75 80

Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His Leu Thr Thr
 85 90 95

Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met Val Ile Met
 100 105 110

Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu Val Lys Lys
 115 120 125

Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile Phe Met Glu
 130 135 140

Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe Ile Asn Thr
 145 150 155 160

Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe Asp Ile Asn
 165 170 175

Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Gly Ala Thr Asn
 180 185 190

Ala His Ala Gly Asn Gln Gly Gly Gln Gln Ala Gly Gly Gly Cys Cys
 195 200 205

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 212 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Rattus norvegicus

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
 1 5 10 15
 Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
 20 25 30
 Pro Val His Asp Leu Thr Met Gly Val Glu Phe Gly Ala Arg Met Ile
 35 40 45
 Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
 50 55 60
 Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
 65 70 75 80
 Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
 85 90 95
 Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
 100 105 110
 Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
 115 120 125
 Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
 130 135 140
 Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
 145 150 155 160
 Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
 165 170 175
 Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
 180 185 190
 Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
 195 200 205
 Gly Gly Cys Cys
 210

(2) INFORMATION FOR SEQ ID NO:19:

64

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 218 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: *Drosophila melanogaster*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met	Ala	Gly	Gly	Asp	Pro	Lys	Trp	Gln	Lys	Asp	Ala	Ala	Asp	Gln	Asn	1	5	10	15
Phe	Asp	Tyr	Met	Phe	Lys	Leu	Leu	Ile	Ile	Gly	Asn	Ser	Ser	Val	Gly	20	25	30	
Lys	Thr	Ser	Phe	Leu	Phe	Arg	Tyr	Ala	Asp	Asp	Ser	Phe	Thr	Ser	Ala	35	40	45	
Phe	Val	Ser	Thr	Val	Gly	Ile	Asp	Phe	Lys	Val	Lys	Thr	Val	Phe	Arg	50	55	60	
His	Asp	Lys	Arg	Val	Lys	Leu	Gln	Ile	Trp	Asp	Thr	Ala	Gly	Gln	Glu	65	70	75	
Arg	Tyr	Arg	Thr	Ile	Thr	Thr	Ala	Tyr	Tyr	Arg	Gly	Ala	Met	Gly	Phe	85	90	95	
Ile	Leu	Met	Tyr	Asp	Val	Thr	Asn	Glu	Asp	Ser	Phe	Asn	Ser	Val	Gln	100	105	110	
Asp	Trp	Val	Thr	Gln	Ile	Lys	Thr	Tyr	Ser	Trp	Asp	Asn	Ala	Gln	Val	115	120	125	
Ile	Leu	Val	Gly	Asn	Lys	Cys	Asp	Met	Glu	Asp	Gln	Arg	Val	Ile	Ser	130	135	140	
Phe	Glu	Arg	Gly	Arg	Gln	Leu	Ala	Asp	Gln	Leu	Gly	Val	Glu	Phe	Phe	145	150	155	
Glu	Thr	Ser	Ala	Lys	Glu	Asn	Val	Asn	Val	Lys	Ala	Val	Phe	Glu	Arg	165	170	175	
Leu	Val	Asp	Ile	Ile	Cys	Lys	Met	Ser	Glu	Ser	Leu	Asp	Ala	Asp	Pro	180	185	190	
Thr	Leu	Val	Gly	Gly	Gly	Gln	Lys	Gly	Gln	Arg	Leu	Thr	Asp	Gln	Pro	195	200	205	
Gln	Gly	Thr	Pro	Asn	Ala	Asn	Cys	Asn	Cys	210	215								

(2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 208 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

65

- (ii) MOLECULE TYPE: protein
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
(A) ORGANISM: *Rattus norvegicus*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met	Ser	Glu	Thr	Tyr	Asp	Phe	Leu	Lys	Phe	Leu	Val	Ile	Gly	Asn	Ala	1	5	10	15
Gly	Thr	Gly	Lys	Ser	Cys	Leu	Leu	His	Gln	Phe	Ile	Glu	Lys	Lys	Phe	20	25	30	
Lys	Asp	Asp	Ser	Asn	His	Thr	Ile	Gly	Val	Glu	Phe	Gly	Gln	Lys	Ile	35	40	45	
Ile	Asn	Val	Gly	Gly	Lys	Tyr	Val	Lys	Leu	Gln	Ile	Trp	Asp	Thr	Ala	50	55	60	
Gly	Gln	Glu	Arg	Phe	Arg	Val	Thr	Thr	Ser	Tyr	Arg	Gly	Ala	Ala	Gly	65	70	75	80
Ala	Leu	Leu	Val	Tyr	Asp	Ile	Thr	Ser	Arg	Glu	Thr	Tyr	Asn	Ala	Leu	85	90	95	
Thr	Asn	Trp	Leu	Thr	Asp	Ala	Arg	Met	Leu	Ala	Ser	Gln	Asn	Ile	Val	100	105	110	
Ile	Cys	Gly	Asn	Lys	Lys	Asp	Leu	Asp	Ala	Asp	Arg	Glu	Val	Thr	Phe	115	120	125	
Leu	Glu	Ala	Ser	Arg	Phe	Ala	Gln	Glu	Asn	Glu	Leu	Met	Phe	Leu	Glu	130	135	140	
Thr	Ser	Ala	Leu	Thr	Gly	Glu	Asn	Val	Glu	Glu	Ala	Phe	Met	Gln	Cys	145	150	155	160
Ala	Arg	Lys	Ile	Leu	Asn	Lys	Ile	Glu	Ser	Gly	Glu	Leu	Asp	Pro	Glu	165	170	175	
Arg	Met	Gly	Ser	Gly	Ile	Gln	Tyr	Gly	Asp	Ala	Ala	Leu	Arg	Gln	Leu	180	185	190	
Arg	Ser	Pro	Arg	Arg	Thr	Gln	Ala	Pro	Ser	Ala	Gln	Glu	Cys	Gly	Cys	195	200	205	

(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 203 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
(A) ORGANISM: *Caenorhabditis elegans*

66

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```

Met Ala Asp Phe Thr Asn Asn Ala Leu Lys Lys Phe Lys Leu Val Phe
 1           5           10           15

Leu Gly Glu Gln Ser Val Gly Lys Thr Ser Ile Ile Thr Arg Phe Met
           20           25           30

Tyr Asp Ser Phe Asp Asn Thr Tyr Gln Ala Thr Ile Gly Ile Asp Phe
           35           40           45

Leu Ser Lys Thr Met Tyr Leu Glu Asp Arg Thr Ile Arg Leu Gln Leu
 50           55           60

Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Ser Leu Ile Pro Ser Tyr
65           70           75           80

Ile Arg Asp Ser Ser Val Ala Val Val Val Tyr Asp Ile Thr Asn Ala
           85           90           95

Asn Ser Phe His Gln Thr Thr Lys Trp Val Asp Asp Val Arg Asn Glu
           100          105          110

Arg Gly Cys Asp Val Ile Ile Val Leu Val Gly Asn Lys Thr Asp Leu
          115          120          125

Ala Asp Lys Arg Gln Val Ser Thr Glu Asp Gly Glu Lys Lys Ala Arg
          130          135          140

Asp Leu Asn Val Met Phe Ile Glu Thr Ser Ala Lys Ala Gly Tyr Asn
145          150          155          160

Val Lys Gln Leu Phe Arg Lys Ile Ala Leu Pro Gly Ile Val Gln Glu
          165          170          175

Glu Thr Pro Glu Gln Pro Asn Ile Val Ile Met Asn Pro Pro Lys Asp
          180          185          190

Ala Glu Glu Ser Gln Gly Arg Gln Cys Pro Cys
          195          200

```

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 207 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```

Met Ser Thr Gly Gly Asp Phe Gly Asn Pro Leu Arg Lys Phe Lys Leu
 1           5           10           15

Val Phe Leu Gly Glu Gln Ser Val Gly Lys Thr Ser Leu Ile Thr Arg
          20           25           30

Phe Met Tyr Asp Ser Phe Asp Asn Thr Tyr Gln Ala Thr Ile Gly Ile

```

67

35	40	45
Asp Phe Leu Ser Lys Thr Met Tyr Leu Glu Asp Arg Thr Val Arg Leu		
50	55	60
Gln Leu Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Ser Leu Ile Pro		
65	70	75
Ser Tyr Ile Arg Asp Ser Thr Val Ala Val Val Val Tyr Asp Ile Thr		
	85	90
Asn Val Asn Ser Phe Gln Gln Thr Thr Lys Trp Ile Asp Asp Val Arg		
	100	105
Thr Glu Arg Gly Ser Asp Val Ile Ile Met Leu Val Gly Asn Lys Thr		
	115	120
Asp Leu Ala Asp Lys Arg Gln Val Ser Ile Glu Glu Gly Glu Arg Lys		
	130	135
Ala Lys Glu Leu Asn Val Met Phe Ile Glu Ser Ala Lys Ala Gly Tyr		
145	150	155
Asn Val Lys Gln Leu Phe Arg Arg Val Ala Ala Ala Leu Pro Gly Met		
	165	170
Glu Ser Thr Gln Asp Arg Ser Arg Glu Asp Met Ile Asp Ile Lys Leu		
	180	185
Glu Lys Pro Gln Glu Gln Pro Val Ser Glu Gly Gly Cys Ser Cys		
	195	200
		205

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 203 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Canis familiaris

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Thr Ser Arg Lys Lys Val Leu Leu Lys Val Ile Ile Leu Gly Asp	
1	15
Ser Gly Val Gly Lys Thr Ser Leu Met Asn Gln Tyr Val Asn Lys Lys	
20	30
Phe Ser Asn Gln Tyr Lys Ala Thr Ile Gly Ala Asp Phe Leu Thr Lys	
35	45
Glu Val Met Val Asp Asp Arg Leu Val Thr Met Gln Ile Trp Asp Thr	
50	60
Ala Gly Gln Glu Arg Phe Gln Ser Leu Gly Val Phe Tyr Arg Gly Ala	
65	75
Asp Cys Cys Val Leu Val Phe Asp Val Thr Ala Pro Asn Thr Phe Lys	

68

				85						90					95			
Thr	Leu	Asp	Ser	Trp	Arg	Asp	Glu	Phe	Leu	Ile	Gln	Ala	Ser	Pro	Arg			
			100					105					110					
Asp	Pro	Glu	Asn	Phe	Pro	Phe	Val	Val	Leu	Gly	Asn	Lys	Ile	Asp	Leu			
		115					120					125						
Glu	Asn	Arg	Gln	Val	Ala	Thr	Lys	Arg	Ala	Gln	Ala	Trp	Cys	Tyr	Ser			
		130				135					140							
Lys	Asn	Asn	Ile	Pro	Tyr	Phe	Glu	Thr	Ser	Ala	Lys	Glu	Ala	Ile	Asn			
145					150				155						160			
Val	Glu	Gln	Ala	Phe	Gln	Thr	Ile	Ala	Arg	Asn	Ala	Leu	Lys	Gln	Glu			
				165					170					175				
Thr	Glu	Val	Glu	Leu	Tyr	Asn	Glu	Phe	Pro	Glu	Pro	Ile	Lys	Leu	Asp			
			180					185					190					
Lys	Asp	Ala	Lys	Thr	Ser	Ala	Glu	Cys	Ser	Cys								
			195				200											

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 202 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met	Thr	Lys	Lys	Lys	Val	Leu	Leu	Lys	Val	Ile	Ile	Leu	Gly	Asp	Ser
1				5					10					15	
Gly	Val	Gly	Lys	Thr	Ser	Leu	Met	Asn	Gln	Tyr	Val	Asn	Lys	Lys	Phe
			20					25				30			
Ser	Asn	Gln	Tyr	Lys	Ala	Thr	Ile	Gly	Ala	Asp	Phe	Leu	Thr	Lys	Glu
		35				40					45				
Leu	Met	Val	Asp	Asp	Arg	Val	Val	Thr	Met	Gln	Ile	Trp	Asp	Thr	Ala
	50				55					60					
Gly	Gln	Glu	Arg	Phe	Gln	Ser	Leu	Gly	Val	Ala	Phe	Tyr	Arg	Gly	Ala
65				70					75					80	
Asp	Cys	Cys	Val	Leu	Cys	Tyr	Asp	Val	Asn	Val	Ala	Lys	Thr	Phe	Glu
			85					90					95		
Asn	Leu	Asp	Ser	Trp	Arg	Asp	Glu	Phe	Leu	Ile	Gln	Ala	Gly	Pro	Arg
			100				105						110		
Asp	Pro	Asp	Asn	Phe	Pro	Phe	Val	Val	Leu	Gly	Asn	Lys	Ile	Asp	Leu
		115					120					125			
Glu	Asn	Gln	Arg	Val	Val	Ser	Gln	Lys	Arg	Ala	Ala	Ser	Trp	Cys	Gln

69

130	135	140
Ser Lys Gly Asn Ile Pro Tyr Phe Glu Thr Ser Ala Lys Glu Ala Ile		
145	150	155
Asn Val Glu Gln Ala Phe Gln Thr Ile Ala Arg Asn Ala Ile Lys Leu		
	165	170
Glu Asp Gly Leu Val Phe Pro Ile Pro Thr Asn Ile Gln Val Ile Pro		
	180	185
Glu Pro Gln Pro Ala Lys Ser Gly Cys Cys		
	195	200

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 205 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Canis familiaris*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Lys Thr Tyr Asp Tyr Leu Phe Lys Leu Leu Leu Ile Gly Asp Ser	
1	5
Gly Val Gly Lys Thr Cys Val Leu Phe Arg Phe Ser Glu Asp Ala Phe	
	20
Asn Ser Thr Phe Ile Ser Thr Ile Gly Ile Asp Phe Lys Ile Arg Thr	
	35
Ile Glu Leu Asp Gly Lys Arg Ile Lys Leu Gln Ile Trp Asp Thr Ala	
	50
Gly Gln Glu Arg Phe Arg Thr Ile Thr Thr Ala Tyr Tyr Arg Ala Met	
	65
Gly Ile Met Leu Val Tyr Asp Ile Thr Asn Glu Lys Ser Phe Asp Asn	
	85
Ile Arg Asn Trp Ile Arg Asn Ile Glu Glu His Ala Ser Ala Asp Val	
	100
Glu Lys Met Ile Leu Gly Asn Lys Cys Asp Val Asn Asp Lys Arg Gln	
	115
Val Ser Lys Glu Arg Gly Glu Lys Leu Ala Leu Asp Tyr Gly Ile Lys	
	130
Phe Met Glu Thr Ser Ala Lys Ala Asn Ile Asn Val Glu Asn Ala Phe	
	145
Phe Thr Leu Ala Arg Asp Ile Lys Ala Lys Met Asp Lys Lys Leu Glu	
	165
Gly Asn Ser Pro Gln Gly Ser Asn Gln Gly Val Lys Ile Thr Pro Asp	

70

	180		185		190
Gln	Gln	Lys	Arg	Ser	Ser
	195			Phe	Phe
			200	Arg	Cys
				Val	Leu
					Leu
					205

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 191 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met	Glu	Glu	Glu	Ile	Leu	Tyr	Lys	Ile	Ile	Leu	Val	Gly	Glu	Ser	Gly
1				5					10					15	
Val	Gly	Lys	Ser	Ser	Ile	Leu	Val	Arg	Phe	Thr	Asp	Asn	Thr	Phe	Ser
			20					25					30		
Gln	His	Phe	Ala	Pro	Thr	Leu	Gly	Val	Phe	Val	Lys	Thr	Ile	Arg	Asn
		35					40					45			
Lys	Glu	Thr	Gly	Gln	Thr	Val	Lys	Leu	Gln	Leu	Trp	Asp	Thr	Ala	Gly
	50					55					60				
Gln	Glu	Arg	Phe	Lys	Ser	Ile	Thr	Gln	Phe	Tyr	Arg	Gly	Ser	His	Gly
65					70					75					80
Val	Ile	Val	Val	Tyr	Asp	Val	Thr	Asp	Pro	Lys	Ser	Phe	Glu	Arg	Leu
				85					90					95	
Lys	Asn	Trp	Val	Glu	Asp	Ile	Asn	Gln	Tyr	Thr	Gln	Asp	Gly	Met	Ile
			100					105					110		
Ile	Ile	Leu	Val	Gly	Asn	Lys	Ser	Asp	Met	Val	Ala	Gln	Arg	Lys	Val
		115					120					125			
Thr	Phe	Glu	Gln	Gly	Gln	Glu	Met	Ala	Glu	Gln	Leu	Lys	Thr	Lys	Phe
	130					135					140				
Leu	Glu	Val	Ser	Ala	Lys	Glu	Asn	Asn	Gly	Val	Thr	Gln	Val	Phe	Asp
145					150					155					160
Leu	Leu	Val	Gln	Asp	Ile	Glu	Ala	Thr	Met	Lys	Asn	Ser	Lys	Val	Ala
			165						170					175	
Gln	Asn	Gln	Leu	Asn	Leu	Ser	Val	Gly	Gln	Glu	Arg	Gly	Cys	Cys	
			180					185					190		

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 189 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: *Caenorhabditis elegans*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```

Met Gln Ala Ile Lys Cys Val Val Val Gly Asp Gly Ala Val Gly Lys
 1           5           10           15
Thr Cys Leu Leu Ile Ser Tyr Thr Thr Asn Ala Phe Pro Gly Glu Tyr
          20           25           30
Ile Pro Thr Val Phe Asp Asn Tyr Ser Ala Asn Val Met Val Asp Gly
          35           40           45
Arg Pro Ile Asn Leu Gly Leu Trp Asp Thr Ala Gly Gln Asp Tyr Asp
          50           55           60
Arg Leu Arg Pro Leu Ser Tyr Pro Gln Thr Asp Val Phe Leu Val Cys
          65           70           75           80
Phe Ala Leu Asn Asn Pro Ala Ser Phe Glu Asn Val Arg Ala Lys Trp
          85           90           95
Tyr Pro Glu Val Ser His His Cys Pro Asn Thr Pro Ile Ile Leu Val
          100          105          110
Gly Thr Lys Ala Asp Leu Arg Glu Asp Asp Thr Val Glu Arg Leu Arg
          115          120          125
Glu Arg Arg Leu Gln Pro Val Ser Gln Thr Gln Gly Tyr Val Met Ala
          130          135          140
Lys Glu Ile Lys Ala Val Lys Tyr Leu Glu Cys Ser Ala Leu Thr Gln
          145          150          155          160
Arg Gly Leu Lys Gln Val Phe Asp Glu Ala Ile Arg Ala Val Val Thr
          165          170          175
Pro Pro Gln Arg Ala Lys Lys Ser Lys Cys Thr Val Leu
          180          185

```

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 191 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: *Dictyostelium discoideum*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```

Met Gln Ala Ile Lys Cys Val Val Val Gly Asp Gly Ala Val Gly Lys

```

72

1		5						10					15			
Thr	Cys	Leu	Leu	Ile	Ser	Tyr	Thr	Thr	Asn	Ala	Phe	Pro	Gly	Glu	Tyr	
		20						25					30			
Ile	Pro	Thr	Val	Phe	Asp	Asn	Tyr	Ser	Ala	Asn	Val	Met	Val	Asp	Gly	
		35					40					45				
Lys	Pro	Ile	Asn	Leu	Gly	Leu	Trp	Asp	Thr	Ala	Gly	Gln	Glu	Asp	Tyr	
	50					55					60					
Asp	Arg	Leu	Arg	Pro	Leu	Ser	Tyr	Pro	Gln	Thr	Asp	Val	Phe	Leu	Ile	
65					70				75						80	
Cys	Phe	Ser	Ile	Ile	Ser	Pro	Ser	Ser	Phe	Glu	Asn	Val	Asn	Gly	Lys	
			85						90					95		
Trp	His	Pro	Glu	Ile	Cys	His	His	Pro	Asn	Val	Pro	Ile	Leu	Val	Gly	
		100						105					110			
Thr	Lys	Leu	Asp	Met	Arg	Asp	Lys	Glu	Thr	Gln	Asp	Arg	Leu	Lys	Glu	
		115					120					125				
Lys	Lys	Leu	Tyr	Pro	Ile	Ser	Tyr	Glu	Gln	Gly	Leu	Ala	Lys	Met	Lys	
	130					135					140					
Glu	Ile	Asn	Ala	Val	Lys	Tyr	Leu	Glu	Cys	Ser	Ala	Leu	Thr	Glu	Lys	
145					150				155						160	
Gly	Leu	Lys	Thr	Val	Phe	Asp	Glu	Ala	Ile	Arg	Ala	Val	Ile	Asn	Pro	
			165						170					175		
Pro	Leu	Ser	Lys	Lys	Lys	Lys	Ser	Ser	Gly	Gly	Cys	Asn	Ile	Leu		
			180					185					190			

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 192 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met	Gln	Ser	Ile	Lys	Leu	Val	Val	Val	Gly	Asp	Gly	Ala	Val	Gly	Lys
1				5					10					15	
Thr	Cys	Leu	Leu	Ile	Ser	Tyr	Thr	Ser	Asn	Ser	Phe	Pro	Thr	Glu	Tyr
		20						25					30		
Val	Pro	Thr	Val	Phe	Asp	Asn	Tyr	Ser	Ala	Asn	Val	Met	Val	Asp	Asn
		35					40					45			
Lys	Thr	Val	Ser	Leu	Gly	Leu	Trp	Asp	Thr	Ala	Gly	Gln	Glu	Asp	Tyr
	50					55					60				
Asp	Arg	Leu	Arg	Pro	Leu	Ser	Tyr	Pro	Gln	Thr	Asp	Val	Phe	Leu	Ile

73

65					70						75				80
Cys	Phe	Ala	Ile	Ile	Ser	Gln	Ser	Tyr	Thr	Asn	Val	Lys	Ser	Lys	Trp
				85					90					95	
Trp	Pro	Glu	Val	Thr	His	His	Cys	Pro	Asn	Cys	Thr	Ile	Leu	Val	Gly
			100					105					110		
Thr	Lys	Cys	Asp	Leu	Arg	Asp	Lys	Glu	Ser	Leu	Glu	Lys	Leu	Arg	Glu
		115					120					125			
Lys	His	Gln	Gln	Pro	Leu	Thr	Phe	Gln	Gln	Gly	Glu	Gln	Met	Ala	Lys
	130					135					140				
Glu	Ile	Lys	Ala	Phe	Cys	Tyr	Met	Glu	Cys	Ser	Ala	Leu	Thr	Gln	Lys
145					150					155					160
Gly	Leu	Lys	Gln	Val	Phe	Asp	Glu	Ala	Ile	Lys	Ala	Val	Ile	Phe	Pro
			165						170					175	
Asp	Arg	Asp	Lys	Ala	Thr	Asn	Lys	Lys	Asn	Ser	Lys	Cys	Ser	Ile	Leu
			180					185					190		

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 185 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met	Ser	Ala	Ala	Glu	Val	Ile	Lys	Leu	Val	Val	Ile	Gly	Gly	Ala	Val
1				5					10					15	
Gly	Lys	Thr	Cys	Leu	Leu	Ile	Tyr	Ala	Asn	Asn	Arg	Phe	Pro	Glu	Asp
			20					25					30		
Tyr	Ile	Pro	Thr	Val	Phe	Asp	Asn	Tyr	Val	Val	Asn	Leu	Thr	Ala	Gly
		35					40					45			
Asp	Arg	Asn	Ile	Glu	Leu	Gly	Leu	Trp	Asp	Thr	Ala	Gly	Glu	Tyr	Asp
	50					55				60					
Lys	Leu	Arg	Pro	Leu	Ser	Tyr	Ala	Asn	Asn	Val	Phe	Leu	Ile	Cys	Phe
65					70					75				80	
Ser	Ile	Asn	Pro	Val	Ser	Phe	Glu	Asn	Val	Tyr	Thr	Lys	Trp	Tyr	Pro
			85					90						95	
Glu	Val	Met	His	Phe	Cys	Pro	Glu	Val	Gln	Ile	Leu	Val	Gly	Thr	Lys
			100					105					110		
Leu	Asp	Thr	Arg	Asp	Asp	Arg	Gly	Val	Leu	Asp	Lys	Leu	Gln	Gln	Thr
			115				120					125			

74

Gly His Lys Pro Ile Thr Thr Glu Gln Gly Asn Asp Leu Ala Arg Arg
 130 135 140
 Ile Lys Ala Ile Lys Tyr Met Glu Cys Ser Ala Lys Thr Ser Gln Asn
 145 150 155 160
 Leu Lys Gln Val Phe Asp Glu Ala Ile Lys Ser Val Leu Phe Ile Lys
 165 170 175
 Lys Lys Lys Ser Lys Cys Ile Val Met
 180 185

(2) INFORMATION FOR SEQ ID NO:31:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 205 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Ala Ala Asn Lys Pro Lys Gly Gln Asn Ser Leu Ala Leu His Lys
 1 5 10 15
 Val Ile Met Val Gly Ser Gly Gly Val Gly Lys Ser Ala Leu Thr Leu
 20 25 30
 Gln Phe Met Tyr Asp Glu Phe Val Glu Asp Tyr Glu Pro Thr Lys Ala
 35 40 45
 Asp Ser Tyr Arg Lys Lys Val Val Leu Asp Gly Glu Glu Val Gln Ile
 50 55 60
 Asp Ile Leu Asp Thr Ala Gly Gln Glu Asp Tyr Ala Ala Ile Arg Asp
 65 70 75 80
 Asn Tyr Phe Arg Ser Gly Glu Gly Phe Leu Cys Val Phe Ser Ile Thr
 85 90 95
 Glu Met Glu Ser Phe Ala Ala Thr Ala Asp Phe Arg Glu Gln Ile Leu
 100 105 110
 Arg Val Lys Glu Asp Glu Asn Val Pro Phe Leu Leu Val Gly Asn Lys
 115 120 125
 Ser Asp Leu Glu Asp Lys Arg Gln Val Ser Val Glu Glu Ala Lys Asn
 130 135 140
 Arg Ala Glu Gln Trp Asn Val Asn Tyr Val Glu Thr Ser Ala Lys Thr
 145 150 155 160
 Arg Ala Asn Val Asp Lys Val Phe Phe Asp Leu Met Arg Glu Ile Arg
 165 170 175
 Ala Arg Lys Met Glu Asp Ser Lys Lys Asn Gly Lys Lys Lys Arg Lys
 180 185 190

75

Ser Leu Ala Lys Arg Ile Arg Glu Arg Cys Cys Ile Leu
 195 200 205

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 204 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

- (vi) ORIGINAL SOURCE:
 (A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Ala Ala Asn Lys Ser Lys Gly Gln Ser Ser Leu Ala Leu His Lys
 1 5 10 15
 Val Ile Met Val Gly Ser Gly Gly Val Gly Lys Ser Ala Leu Thr Leu
 20 25 30
 Gln Phe Met Tyr Asp Glu Phe Val Glu Asp Tyr Glu Pro Thr Lys Ala
 35 40 45
 Asp Ser Tyr Arg Lys Lys Val Val Leu Asp Gly Glu Glu Val Ile Asp
 50 55 60
 Ile Leu Asp Thr Ala Gly Gln Glu Asp Tyr Ala Ile Arg Asp Asn Tyr
 65 70 75 80
 Phe Arg Ser Gly Glu Gly Phe Leu Leu Val Phe Ser Ile Thr Glu His
 85 90 95
 Glu Ser Phe Thr Ala Thr Ala Glu Phe Arg Glu Gln Ile Leu Arg Val
 100 105 110
 Lys Ala Glu Glu Asp Lys Ile Pro Leu Leu Val Val Gly Asn Lys Ser
 115 120 125
 Asp Leu Glu Glu Arg Arg Gln Val Pro Val Glu Glu Ala Arg Ser Lys
 130 135 140
 Ala Glu Glu Trp Gly Val Gln Tyr Val Glu Thr Ser Ala Lys Thr Arg
 145 150 155 160
 Ala Asn Val Asp Lys Val Phe Phe Asp Leu Met Arg Glu Ile Arg Thr
 165 170 175
 Lys Lys Met Ser Glu Asn Lys Asp Lys Asn Gly Lys Lys Ser Ser Lys
 180 185 190
 Asn Lys Lys Ser Phe Lys Glu Arg Cys Cys Leu Leu
 195 200

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 200 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single

76

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Discopyge ommata

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```

Met Ala Ala Asn Lys Asn Lys Asn Gln Ser Ser Leu Leu Lys Val Ile
1           5           10           15
Met Val Gly Ser Gly Gly Val Gly Lys Ser Ala Leu Thr Leu Gln Phe
20           25           30
Met Tyr Asp Glu Phe Val Glu Asp Tyr Glu Pro Thr Lys Ala Asp Ser
35           40           45
Tyr Arg Lys Lys Val Val Leu Asp Gly Glu Val Gln Ile Asp Ile Leu
50           55           60
Asp Thr Ala Gly Gln Glu Asp Tyr Ala Ile Arg Asp Asn Tyr Phe Arg
65           70           75           80
Ser Gly Glu Gly Phe Leu Cys Val Phe Ser Ile Glu Gln Glu Ser Phe
85           90           95
Thr Ala Thr Val Glu Phe Arg Glu Gln Ile Leu Arg Val Lys Glu Glu
100          105          110
Asp Lys Ile Pro Leu Leu Leu Val Gly Asn Lys Ser Asp Leu Glu Asp
115          120          125
Arg Arg Gln Val Ser Ile Glu Glu Ala Arg Ser Lys Ala Glu Glu Trp
130          135          140
Gly Val Gln Tyr Val Glu Thr Ser Ala Lys Thr Arg Ala Asn Val Asp
145          150          155          160
Lys Val Phe Phe Asp Leu Met Arg Glu Val Arg Ala Lys Lys Met Ser
165          170          175
Glu Asn Lys Asp Lys Asn Gly Lys Lys Ser Ser Arg Asn Lys Lys Ser
180          185          190
Leu Arg Glu Arg Cys Cys Ile Leu
195          200

```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 194 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Discopyge ommata

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Ala Lys Lys Thr Tyr Asp Leu Leu Phe Lys Leu Leu Leu Ile Gly
 1 5 10 15
 Asp Ser Gly Val Gly Lys Thr Cys Val Leu Phe Arg Phe Ser Asp Asp
 20 25 30
 Ala Phe Asn Thr Thr Phe Ile Ser Thr Ile Gly Ile Asp Phe Lys Ile
 35 40 45
 Lys Thr Val Glu Leu His Gly Lys Lys Ile Lys Leu Gln Ile Trp Asp
 50 55 60
 Thr Ala Gly Gln Glu Arg Phe His Thr Ile Thr Ser Tyr Tyr Arg Gly
 65 70 75 80
 Ala Met Gly Ile Met Leu Val Tyr Asp Ile Thr Asn Ala Lys Ser Phe
 85 90 95
 Glu Asn Ile Ser Lys Trp Leu Arg Asn Ile Asp Glu His Ala Asn Glu
 100 105 110
 Asp Val Glu Arg Met Leu Leu Gly Asn Lys Asp Met Glu Asp Lys Arg
 115 120 125
 Val Val Leu Lys Ser Lys Gly Gln Ile Ala Glu His Ala Ile Arg Phe
 130 135 140
 Phe Glu Thr Ser Ala Lys Ala Asn Ile Asn Ile Glu Lys Ala Phe Leu
 145 150 155 160
 Thr Leu Ala Glu Asp Ile Leu Gln Lys Thr Pro Val Lys Glu Pro Asp
 165 170 175
 Arg Glu Asn Val Asp Ile Ser Thr Gly Gly Gly Gly Leu Lys Lys Cys
 180 185 190
 Cys Ser

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 207 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Discopyge ommata*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Met Lys Thr Tyr Asp Tyr Leu Phe Lys Leu Leu Leu Ile Gly Asp Ser
 1 5 10 15
 Gly Val Gly Lys Thr Cys Leu Leu Phe Arg Phe Ser Glu Asp Ala Phe
 20 25 30

78

```

Asn Thr Thr Phe Ile Ser Thr Ile Gly Ile Asp Phe Lys Ile Arg Thr
   35           40           45
Val Glu Leu Asp Gly Lys Lys Ile Lys Leu Gln Ile Trp Asp Thr Ala
   50           55           60
Gly Gln Glu Arg Phe Arg Thr Ile Thr Ala Tyr Tyr Arg Gly Ala Met
   65           70           75           80
Gly Ile Met Lys Val Asp Ile Thr Asn Glu Lys Ser Phe Asp Asn Ile
           85           90           95
Lys Asn Trp Ile Arg Asn Ile Glu Glu His Ala Ser Ser Asp Val Glu
           100          105          110
Arg Met Ile Leu Gly Asn Lys Cys Asp Met Asn Glu Lys Arg Gln Val
           115          120          125
Ser Lys Glu Arg Gly Glu Lys Leu Ala Ile Asp Tyr Gly Ile Lys Phe
           130          135          140
Leu Glu Thr Ser Ala Lys Ser Ser Ile Asn Val Glu Glu Ala Phe Ile
           145          150          155          160
Thr Leu Ala Arg Asp Ile Met Thr Lys Leu Asn Lys Lys Met Asn Glu
           165          170          175
Asn Ser Leu Gln Glu Ala Val Asp Lys Leu Lys Ser Pro Pro Lys Lys
           180          185          190
Pro Ser Gln Lys Lys Lys Gln Leu Ser Phe Arg Cys Ser Leu Leu
           195          200          205

```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Discopyge ommata

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```

Met Gly Thr Arg Asp Asp Glu Tyr Asp Tyr Leu Phe Lys Val Val Leu
  1           5           10
Ile Gly Asp Ser Gly Val Gly Lys Ser Asn Leu Leu Ser Arg Phe Thr
           20           25           30
Arg Glu Phe Asn Leu Glu Ser Lys Ser Thr Ile Gly Val Glu Phe Ala
           35           40           45
Thr Arg Ser Ile Gln Val Asp Gly Lys Thr Ile Lys Gln Ile Trp Asp
           50           55           60
Thr Gly Gln Glu Arg Tyr Arg Ala Ile Thr Ser Ala Tyr Tyr Arg Gly
           65           70           75           80

```

79

Ala Val Gly Ala Leu Leu Val Tyr Asp Ile Ala Lys His Leu Thr Tyr
85 90 95

Glu Asn Val Glu Arg Trp Leu Lys Glu Leu Arg Asp His Ala Asp Asn
100 105 110

Asn Ile Val Ile Met Leu Val Gly Asn Lys Ser Asp Leu Arg His Leu
115 120 125

Arg Val Pro Thr Asp Ala Arg Ala Phe Ala Glu Lys Asn Asn Leu Ser
130 135 140

Phe Ile Glu Thr Ser Ala Leu Asp Ser Thr Asn Val Glu Glu Ala Phe
145 150 155 160

Lys Asn Ile Leu Thr Glu Ile Tyr Arg Ile Val Ser Gln Lys Gln Ile
165 170 175

Ser Asp Arg Ser Ala His Asp Glu Ser Pro Gly Asn Asn Val Val Asp
180 185 190

Ile Ser Val Pro Pro Thr Thr Asp Gly Gln Lys Ser Asn Lys Leu Gln
195 200 205

Cys Cys Gln Asn Met
210

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 184 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Met Pro Leu Arg Phe Lys Ile Val Val Leu Gly Ser Gly Gly Val Gly
1 5 10 15

Lys Ser Ala Leu Thr Val Gln Phe Val Gln Gly Ile Phe Val Glu Lys
20 25 30

Tyr Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Glu Val Asp
35 40 45

Ser Asn Gln Cys Met Leu Glu Ile Leu Asp Thr Ala Gly Thr Glu Gln
50 55 60

Phe Thr Met Arg Asp Leu Tyr Met Lys Asn Gly Gln Gly Phe Val Leu
65 70 75 80

Val Tyr Ser Ile Ile Ser Asn Ser Thr Phe Asn Glu Leu Pro Asp Leu
85 90 95

Arg Glu Gln Ile Leu Arg Val Lys Asp Cys Glu Asp Val Pro Met Val
100 105 110

80

Leu Val Gly Asn Lys Cys Asp Leu His Asp Gln Arg Val Ile Ser Thr
 115 120 125
 Glu Gln Gly Glu Glu Leu Ala Arg Lys Phe Gly Asp Cys Tyr Phe Leu
 130 135 140
 Glu Ala Ser Ala Lys Asn Lys Val Asn Val Glu Gln Ile Phe Tyr Asn
 145 150 155 160
 Leu Ile Arg Gln Ile Asn Arg Lys Asn Pro Val Gly Pro Pro Ser Lys
 165 170 175
 Ala Lys Ser Lys Cys Ala Leu Leu
 180

(2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 179 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

- (vi) ORIGINAL SOURCE:
- (A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Met Arg Glu Tyr Lys Val Val Val Leu Gly Ser Gly Gly Val Gly Lys
 1 5 10 15
 Ser Ala Leu Thr Val Gln Phe Val Thr Gly Thr Phe Ile Glu Lys Tyr
 20 25 30
 Asp Pro Thr Ile Glu Asp Phe Tyr Arg Lys Glu Ile Glu Val Asp Ser
 35 40 45
 Ser Pro Ser Val Leu Glu Ile Leu Asp Thr Ala Gly Thr Glu Gln Phe
 50 55 60
 Ala Ser Arg Asp Leu Tyr Ile Lys Asn Gly Gln Gly Phe Ile Leu Val
 65 70 75 80
 Tyr Ser Leu Val Asn Gln Gln Phe Gln Asp Ile Lys Pro Met Arg Asp
 85 90 95
 Gln Ile Ile Arg Val Lys Tyr Glu Lys Val Pro Val Ile Leu Val Gly
 100 105 110
 Asn Lys Val Asp Leu Glu Ser Glu Arg Glu Val Ser Ser Ser Glu Gly
 115 120 125
 Arg Ala Leu Ala Glu Glu Trp Gly Cys Pro Phe Met Glu Thr Ser Ala
 130 135 140
 Lys Ser Lys Thr Met Val Asp Glu Leu Phe Ala Glu Ile Val Arg Gln
 145 150 155 160
 Met Asn Tyr Ala Ala Gln Pro Asp Lys Asp Asp Pro Cys Cys Ser Ala
 165 170 175

Cys Asn Gln

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 183 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```

Met Arg Glu Tyr Lys Val Val Val Leu Gly Ser Gly Gly Val Gly Lys
 1           5           10           15
Ser Ala Leu Thr Val Gln Phe Val Thr Gly Ser Phe Ile Glu Lys Tyr
          20           25           30
Asp Pro Thr Ile Glu Asp Phe Tyr Arg Lys Glu Ile Glu Val Asp Ser
          35           40           45
Ser Pro Ser Val Leu Glu Ile Leu Asp Thr Ala Gly Thr Glu Gln Phe
 50           55           60
Ala Ser Met Arg Asp Leu Tyr Ile Lys Asn Gly Gln Gly Phe Ile Leu
 65           70           75           80
Val Tyr Ser Leu Val Asn Gln Gln Ser Phe Gln Asp Ile Lys Pro Met
          85           90           95
Arg Asp Gln Ile Ile Arg Val Lys Arg Tyr Glu Arg Val Pro Met Ile
          100          105          110
Leu Val Gly Asn Lys Val Asp Leu Glu Gly Glu Arg Glu Val Ser Tyr
          115          120          125
Gly Glu Gly Lys Ala Leu Ala Glu Glu Trp Ser Cys Pro Phe Met Glu
          130          135          140
Thr Ser Ala Lys Asn Lys Ala Ser Val Asp Glu Leu Phe Ala Glu Ile
          145          150          155          160
Val Arg Gln Met Asn Tyr Ala Ala Gln Ser Asn Gly Asp Glu Gly Cys
          165          170          175
Cys Ser Ala Cys Val Ile Leu
          180

```

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 184 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

82

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Discopyge ommata*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

```

Met Arg Glu Tyr Lys Leu Val Val Leu Gly Ser Gly Gly Val Gly Lys
 1           5          10
Ser Ala Leu Thr Val Gln Phe Val Gln Gly Ile Phe Val Glu Lys Tyr
          20          25          30
Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Glu Val Asp Cys
          35          40          45
Gln Pro Cys Met Leu Glu Ile Leu Asp Thr Ala Gly Thr Glu Gln Phe
 50          55          60
Thr Ala Met Arg Asp Leu Tyr Met Lys Asn Gly Gln Gly Phe Ala Leu
 65          70          75          80
Val Tyr Ser Ile Thr Ala Gln Ser Thr Phe Asn Asp Leu Gln Asp Leu
          85          90          95
Arg Glu Gln Ile Leu Arg Val Lys Asp Thr Glu Asp Val Pro Met Ile
          100          105          110
Leu Val Gly Asn Lys Cys Asp Leu Glu Asp Glu Arg Val Val Gly Lys
          115          120          125
Glu Gln Gly Gln Asn Leu Ala Arg Gln Trp Asn Asn Cys Ala Phe Leu
          130          135          140
Glu Ser Ser Ala Lys Ser Lys Ile Asn Val Asn Glu Ile Phe Tyr Asp
          145          150          155          160
Leu Val Arg Gln Ile Asn Arg Lys Ala Pro Val Glu Lys Cys Lys Lys
          165          170          175
Lys Lys Ser Gln Cys Thr Leu Leu
          180

```

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 180 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Homo sapiens*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

```

Met Arg Glu Tyr Lys Leu Val Val Gly Ser Gly Gly Val Gly Lys Ser
 1           5          10          15

```

83

Ala Leu Thr Val Gln Phe Val Gln Gly Phe Val Glu Lys Tyr Asp Pro
 20 25 30

Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Glu Val Asp Cys Gln Gln
 35 40 45

Cys Met Leu Glu Asp Thr Ala Gly Thr Glu Gln Phe Thr Ala Met Arg
 50 55 60

Asp Leu Tyr Met Lys Asn Gly Gln Gly Phe Ala Leu Val Tyr Ser Ile
 65 70 75 80

Thr Ala Gln Ser Thr Phe Asn Asp Leu Gln Asp Leu Arg Glu Gln Ile
 85 90 95

Leu Arg Val Lys Asp Thr Glu Asp Val Pro Met Ile Leu Val Gly Asn
 100 105 110

Lys Cys Asp Leu Glu Asp Glu Arg Val Val Gly Lys Glu Gln Gly Gln
 115 120 125

Asn Leu Ala Arg Gln Trp Cys Asn Cys Ala Phe Leu Glu Ser Ser Ala
 130 135 140

Lys Ser Lys Ile Asn Val Asn Glu Ile Phe Tyr Asp Leu Val Arg Gln
 145 150 155 160

Ile Asn Arg Lys Thr Pro Val Glu Lys Lys Lys Pro Lys Lys Lys Ser
 165 170 175

Cys Leu Leu Leu
 180

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 179 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Met Arg Glu Tyr Lys Leu Val Val Leu Gly Ser Gly Gly Val Gly Lys
 1 5 10 15

Ser Ala Leu Thr Val Gln Phe Val Gln Gly Ile Phe Val Glu Lys Tyr
 20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Glu Val Asp Ala
 35 40 45

Gln Gln Cys Met Leu Glu Ile Leu Asp Thr Ala Gly Thr Glu Gln Phe
 50 55 60

Thr Ala Met Arg Asp Leu Tyr Met Lys Asn Gly Gln Gly Phe Ala Leu
 65 70 75 80

84

Val Tyr Ser Ile Thr Ala Gln Ser Thr Phe Asn Asp Leu Gln Asp Leu
85 90 95
Arg Glu Gln Ile Leu Arg Val Lys Asp Thr Asp Asp Val Pro Met Ile
100 105 110
Leu Val Gly Asn Lys Cys Asp Leu Glu Asp Glu Arg Val Val Gly Lys
115 120 125
Glu Gln Gly Gln Asn Leu Ala Arg Gln Trp Asn Asn Cys Ala Phe Leu
130 135 140
Glu Ser Ser Ala Lys Ser Lys Ile Asn Val Glu Ile Phe Tyr Asp Leu
145 150 155 160
Val Arg Gln Ile Asn Arg Lys Thr Pro Val Pro Gly Lys Ala Arg Lys
165 170 175
Lys Ser Ser

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 184 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Drosophila melanogaster*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Met Arg Glu Tyr Lys Ile Val Val Leu Gly Ser Gly Gly Val Gly Lys
1 5 10 15
Ser Ala Leu Thr Val Gln Phe Val Gln Cys Ile Phe Val Glu Lys Tyr
20 25 30
Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Glu Val Asp Gly
35 40 45
Gln Gln Cys Met Leu Glu Ile Leu Asp Thr Ala Gly Thr Glu Gln Phe
50 55 60
Thr Ala Met Arg Asp Leu Tyr Met Lys Asn Gly Gln Gly Phe Val Leu
65 70 75 80
Val Tyr Ser Ile Thr Ala Gln Ser Thr Phe Asn Asp Leu Gln Asp Leu
85 90 95
Arg Glu Gln Ile Leu Arg Val Lys Asp Thr Asp Asp Val Pro Met Val
100 105 110
Leu Val Gly Asn Lys Cys Asp Leu Glu Glu Glu Arg Val Val Gly Lys
115 120 125
Glu Leu Gly Lys Asn Leu Ala Thr Gln Phe Asn Cys Ala Phe Met Glu
130 135 140

85

Thr Ser Ala Lys Ala Lys Val Asn Val Asn Asp Ile Phe Tyr Asp Leu
 145 150 155 160
 Val Arg Gln Ile Asn Lys Lys Ser Pro Glu Lys Lys Gln Lys Lys Pro
 165 170 175
 Lys Lys Ser Leu Cys Val Leu Leu
 180

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 182 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Met Thr Glu Tyr Lys Leu Val Ile Val Gly Gly Gly Gly Val Gly Lys
 1 5 10 15
 Ser Leu Thr Ile Gln Leu Ile Gln Asn His Phe Asp Glu Tyr Asp Pro
 20 25 30
 Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Ser Ile Asp Asp Glu Thr
 35 40 45
 Cys Leu Leu Ile Leu Asp Thr Ala Gly Gln Glu Glu Ser Ala Met Arg
 50 55 60
 Asp Gln Tyr Met Arg Thr Gly Gln Gly Phe Leu Cys Val Tyr Ser Ile
 65 70 75 80
 Thr Ser Arg Ser Ser Tyr Asp Glu Ile Ala Ser Phe Arg Glu Gln Ile
 85 90 95
 Leu Arg Val Lys Asp Lys Asp Arg Val Pro Leu Ile Leu Val Gly Asn
 100 105 110
 Lys Ala Asp Leu Asp His Glu Arg Gln Val Ser Val Asn Glu Gly Gln
 115 120 125
 Glu Leu Ala Lys Asp Ser Leu Ser Phe His Glu Ser Ser Ala Lys Ser
 130 135 140
 Arg Ile Asn Val Glu Glu Ala Phe Tyr Ser Leu Val Arg Glu Ile Arg
 145 150 155 160
 Lys Glu Leu Lys Gly Asp Gln Ser Ser Gly Lys Ala Gln Lys Lys Lys
 165 170 175
 Lys Gln Cys Leu Ile Leu
 180

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

86

- (A) LENGTH: 190 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```

Met Ser Val Ser Asn Glu Tyr Lys Leu Val Val Gly Gly Gly Gly Val
1           5           10           15
Gly Lys Ser Ala Leu Thr Ile Gln Phe Gln Asn His Phe Ile Glu Glu
20           25           30
Tyr Asp Pro Thr Ile Glu Asp Ser Tyr Arg Arg Gln Cys Gln Val Asp
35           40           45
Glu Asp Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Asp Asp
50           55           60
Tyr Ser Met Arg Asp Gln Tyr Met Arg Thr Gly Gln Gly Phe Leu Val
65           70           75           80
Tyr Asp Val Ser Arg Thr Ser Phe Glu Glu Ile Asn Val Val Glu Gln
85           90           95
Ile Arg Val Lys Asp Asn Asp Lys Val Pro Ile Val Leu Val Gly Asn
100          105          110
Lys Cys Asp Leu Glu Asn Leu Arg Glu Val Thr Glu Gly Glu Gly Ser
115          120          125
Glu Leu Ala Lys Ser Phe Ser Val Pro Phe Leu Glu Thr Ser Ala Lys
130          135          140
Lys Arg Leu Asn Val Asp Glu Cys Phe Phe Glu Val Val Arg Glu Ile
145          150          155          160
Lys Lys Ser Leu Lys Glu Pro Gly Arg Ser Lys Lys Asp Lys Lys Gly
165          170          175
Gly Ile Leu Lys Lys Phe Lys Gly Gly Asp Cys Leu Ile Leu
180          185          190

```

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 188 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```

Met Ser Lys Leu Leu Lys Leu Val Ile Val Gly Asp Gly Gly Val Gly
1           5           10
Lys Ser Ala Leu Thr Ile Gln Leu Thr Gln Asn Gln Phe Ile Ala Glu
20          25          30
Tyr Asp Pro Thr Ile Glu Asn Ser Tyr Arg Lys Gln Val Asn Ile Asp
35          40          45
Glu Glu Val Tyr Met Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu
50          55          60
Tyr Ser Ala Met Arg Asp Gln Tyr Ile Arg Ser Gly Arg Gly Phe Leu
65          70          75          80
Ile Val Tyr Ser Ile Ile Ser Arg Ala Ser Phe Glu Ala Val Thr Thr
85          90          95
Phe Arg Glu Gln Ile Leu Arg Val Lys Asp Leu Ser Thr Tyr Pro Ile
100         105
Val Ile Ile Gly Asn Lys Ala Asp Leu Pro Asp Lys Asp Arg Lys Val
115        120        125
Pro Pro Met Glu Gly Lys Glu Leu Ala Lys Phe Gly Ala Pro Phe Leu
130        135        140
Glu Thr Ser Ala Lys Ser Arg Val Asn Val Glu Glu Ala Phe Phe Thr
145        150        155        160
Leu Val Arg Glu Ile Lys Arg Trp Asn Gln Asn Pro Gln Asn Glu Glu
165        170        175
Met Leu Pro Pro Lys Lys Arg Gly Cys Ile Ile Leu
180        185

```

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 188 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Dictyostelium discoideum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```

Met Glu Tyr Lys Leu Val Ile Val Gly Gly Gly Gly Val Gly Lys Ser
1           5           10
Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Ile Asp Glu Tyr Asp
20          25          30
Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Thr Ile Asp Glu Glu
35          40          45

```

88

Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr Ser
 50 55 60
 Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Gln Gly Phe Leu Cys Val
 65 70 75 80
 Tyr Ser Ile Thr Ser Arg Ser Ser Phe Asp Glu Ile Ala Ser Phe Arg
 85 90 95
 Glu Gln Ile Leu Arg Val Lys Asp Lys Asp Arg Val Pro Met Ile Val
 100 105 110
 Val Gly Asn Lys Cys Asp Leu Glu Ser Asp Arg Gln Val Thr Thr Gly
 115 120 125
 Glu Gly Gln Asp Leu Ala Lys Ser Phe Gly Ser Pro Phe Leu Glu Thr
 130 135 140
 Ser Ala Lys Ile Arg Val Asn Val Glu Glu Ala Phe Tyr Ser Leu Val
 145 150 155 160
 Arg Glu Ile Arg Lys Asp Leu Lys Gly Asp Ser Lys Pro Glu Lys Gly
 165 170 175
 Lys Lys Lys Arg Pro Leu Lys Ala Cys Thr Leu Leu
 180 185

(2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 204 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
 - (A) ORGANISM: *Caenorhabditis elegans*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Met Ser Ser Ser Leu Gln Ser Asn Arg Gln Ser Leu Asn Arg Lys Val
 1 5 10 15
 Ala Val Met Gly Tyr Pro His Val Gly Lys Ser Ala Leu Val Leu Arg
 20 25 30
 Phe Thr Gln Asn Ile Phe Pro Glu Arg Tyr Glu Ser Thr Ile Glu Asp
 35 40 45
 Gln His Ser Lys His Ile Ala Ala Phe His Arg Asp Tyr His Leu Arg
 50 55 60
 Val Thr Asp Thr Ala Gly Gln Gln Glu Tyr Thr Val Phe Pro Arg Ser
 65 70 75 80
 Cys Ser Leu Asp Ile Asn Gly Phe Ile Leu Val Tyr Ala Ile Asp Asp
 85 90 95
 Arg Lys Ser Phe Glu Met Cys Ser Asn Ile Tyr Glu Lys Ile Val Arg
 100 105 110

89

```

Thr Tyr Gly Asp Thr Ser Ile Pro Ile Val Ile Val Gly Lys Thr Asp
      115                      120                      125
Leu Ser Thr Gln Val Val Arg Ala Glu Glu Gly Glu Glu Leu Ala Arg
      130                      135                      140
Gln Trp Asp Ala Lys Phe Val Glu Ile Thr Ala Arg Glu Ser Asn Arg
      145                      150                      155                      160
Val His Glu Val Phe Glu Leu Leu Leu Arg Glu Ile Glu Ile Ser Arg
                      165                      170                      175
Gly Asn Leu Ser Pro Thr Glu Arg Pro Asn Gly Asn Ser Pro Lys Arg
                      180                      185                      190
Pro Phe Lys Asp Asp Gly Lys Pro Cys Ser Ile Ser
      195                      200

```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 215 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Coprinus cinereus*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```

Met Ala Ala Arg Ala Gln Phe Leu Arg Glu Tyr Lys Leu Val Val Val
1      5      10      15
Gly Gly Gly Gly Val Gly Lys Ser Ala Leu Thr Ile Gln Phe Ile Gln
      20      25      30
Ser His Phe Val Asp Glu Tyr Asp Pro Thr Ile Glu Asp Ser Tyr Arg
      35      40      45
Lys Gln Cys Ile Ile Asp Asp Glu Val Ala Leu Leu Asp Val Leu Asp
      50      55      60
Thr Ala Gly Gln Glu Glu Tyr Gly Ala Met Arg Glu Gln Tyr Met Arg
      65      70      75      80
Thr Gly Glu Gly Phe Leu Leu Val Tyr Ser Ile Thr Ser Arg Asn Ser
      85      90      95
Phe Glu Glu Ile Ser Ile Phe His Gln Gln Ile Leu Arg Val Lys Asp
      100     105     110
Gln Asp Ser Phe Pro Val Ile Val Val Ala Asn Lys Cys Asp Leu Glu
      115     120     125
Tyr Glu Arg Gln Val Gly Met Asn Glu Gly Arg Asp Leu Ala Lys His
      130     135     140
Phe Gly Cys Lys Phe Ile Glu Thr Ser Ala Lys Gln Arg Ile Asn Val
      145     150     155     160

```

90

Asp Glu Ala Phe Ser Asn Leu Val Arg Glu Ile Arg Lys Tyr Asn Arg
 165 170 175

Glu Gln Gln Thr Gly Arg Pro Ala Ile Ala Ala Gly Gly Gly Gly Pro
 180 185 190

Ala Gly Ser Tyr Thr Gln Asp Arg His His Asp Glu Ala Pro Gly Cys
 195 200 205

Cys Ala Gly Cys Val Ile Ala
 210 215

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 206 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Geodia cydonium

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Met Thr Glu Tyr Lys Ile Val Val Gly Gly Gly Leu Val Gly Lys Ser
 1 5 10 15

Ala Leu Thr Leu Gln Leu Val Gln Val Cys Ile Lys Asp Gln Tyr Tyr
 20 25 30

Leu Ile Glu Phe Gln Asn Asn Gln Phe Gln Phe Glu Asn Leu Gln Asn
 35 40 45

His Tyr Ile Asp Tyr Asp Pro Thr Val Glu Asp Ser Arg Arg Glu Val
 50 55 60

Ser Ile Asp Asp Gln Thr Cys Leu Asn Ile Leu Asp Thr Ala Gly Gln
 65 70 75 80

Gln His Ser Asn Ala Gln Ser Met Asp Ala His Trp Ser Thr Val Phe
 85 90 95

Val Cys Leu Phe Asn Tyr Phe Asn Ile Thr Ser Met Tyr Asp Glu Ile
 100 105 110

Ala Ser Phe Arg Glu Gln Ile Leu Arg Val Lys Asp Gly Ala Lys Asp
 115 120 125

Leu Val Pro Leu Ile Leu Ile Ile Asn Lys Ala Asp Leu Asp His Glu
 130 135 140

Ser Gln Gly Ser Gly Asn Glu Gly Gln Leu Ala Lys Asp Ser Leu Ser
 145 150 155 160

Phe His Gln Ser Ser Ala Lys Ser Arg Ile Asn Leu Glu Glu Ile Pro
 165 170 175

Tyr Ser Leu Val Arg Glu Leu Arg Lys Glu Leu Lys Leu Asp Gln Ser
 180 185 190

91

Ser Gly Lys Ala Gln Lys Lys Lys Lys Gln Cys Leu Ile Ile
 195 200 205

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 198 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Canis familiaris

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Met Lys Lys Thr Tyr Asp Leu Leu Phe Lys Leu Leu Leu Ile Gly Asp
 1 5 10 15
 Ser Gly Val Gly Lys Thr Cys Val Leu Phe Arg Phe Ser Asp Asp Ala
 20 25 30
 Phe Asn Thr Thr Phe Ile Ser Ile Gly Ile Asp Phe Lys Ile Lys Thr
 35 40 45
 Val Glu Leu Gln Gly Lys Lys Ile Lys Leu Gln Ile Trp Asp Thr Ala
 50 55 60
 Gly Gln Glu Arg Phe His Thr Ile Thr Thr Ser Tyr Tyr Arg Gly Ala
 65 70 75 80
 Met Gly Ile Met Leu Val Tyr Asp Ile Thr Asn Gly Lys Ser Phe Glu
 85 90 95
 Asn Ile Ser Lys Trp Leu Arg Asn Ile Asp Glu His Ala Asn Glu Asp
 100 105 110
 Val Glu Arg Met Leu Leu Gly Asn Lys Cys Asp Met Asp Asp Lys Arg
 115 120 125
 Val Val Pro Lys Gly Lys Gly Glu Gln Ile Ala Arg Glu His Gly Ile
 130 135 140
 Arg Phe Phe Glu Thr Ser Ala Lys Val Asn Ile Asn Ile Glu Lys Ala
 145 150 155 160
 Phe Leu Thr Leu Ala Glu Asp Ile Leu Arg Lys Thr Pro Val Lys Glu
 165 170 175
 Pro Asn Ser Glu Asn Val Asp Ile Ser Ser Gly Gly Gly Val Thr Gly
 180 185 190
 Trp Lys Ser Lys Cys Cys
 195

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 214 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

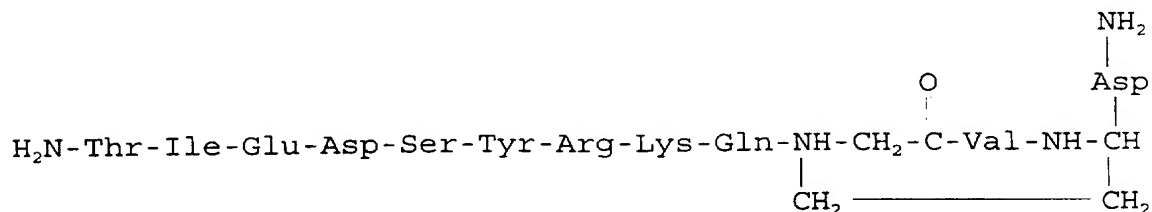
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

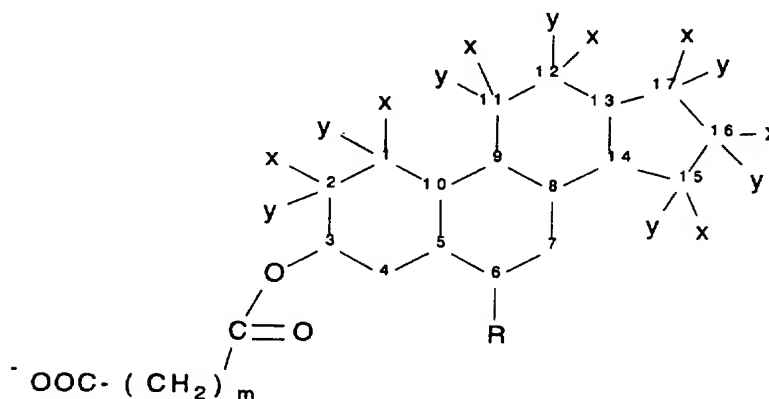
[illegible]

We claim:

1. A composition comprising at least one component selected from the group consisting of a peptide having an amino acid sequence selected from the group consisting of Val-Val-Ile, Ile-Lys-Arg-Val-Lys-Asp (SEQ ID NO:1), Lys-Cys-Asp-Leu-Ala (SEQ ID NO:2), Cys-Asp-Leu-Ala-Ala-Arg-Thr (SEQ ID NO:3) and Asp-Leu-Ala-Ala (SEQ ID NO:4) or a physiologically acceptable salt of said peptide, a cyclized peptide having a formula selected from the group consisting of cyclo [-R(1) R(2) Thr-Ile-Glu-Asp-Ser-Tyr-Arg-Lys-Gln-Val-Val-Ile-Asp R(3) R(4)-], cyclo [-R(1) R(2) Val-Val-Ile R(3) R(4)-], cyclo [-R(1) R(2) Tyr-Arg-Glu-Gln-Ile-Lys-Arg-Val-Lys-Asp-Ser-Asp-Asp-Val-Pro R(3) R(4)-], cyclo [-R(1) R(2) Lys-Arg-Val R(3) R(4)-], cyclo [-R(1) R(2) Ile-Lys-Arg-Val-Lys-Asp R(3) R(4)-], cyclo [-R(1) R(2) Gly-Asn-Lys-Cys-Asp-Leu-Ala-Ala-Arg-Thr-Val-Glu R(3) R(4)-], cyclo [-R(1) R(2) Lys-Cys-Asp-Leu-Ala R(3) R(4)-], cyclo [-R(1) R(2) Cys-Asp-Leu-Ala-Ala-Arg-Thr R(3) R(4)-], cyclo [-R(1) R(2) Asp-Leu-Ala R(3) R(4)-], cyclo [-R(1) R(2) D-Thr-Ile-Glu-Asp-Ser-Tyr-Arg-Lys-Gln-Val-D-Val-Ile-Asp R(3) R(4)-], cyclo [-R(1) R(2) D-Val-D-Val-D-Ile R(3) R(4)-], cyclo [-R(1) R(2) D-Tyr-Arg-Glu-Gln-Ile-Lys-Arg-Val-Lys-Asp-D-Ser-Asp-D-Asp-Val-Pro R(3) R(4)-], cyclo [-R(1) R(2) D-Lys-D-Arg-D-Val-R(3) R(4)-], cyclo [-R(1) R(2) D-Ile-Lys-Arg-Val-Lys-D-Asp-R(3) R(4)-], cyclo [-R(1) R(2) Gly-D-Asn-Lys-Cys-Asp-Leu-D-Ala-Ala-Arg-Thr-D-Val-Glu R(3) R(4)-], cyclo [-R(1) R(2) D-Lys-Cys-Asp-Leu-D-Ala R(3) R(4)-], cyclo [-R(1) R(2) Cys-Asp-Leu-Ala-Ala-Arg-D-Thr R(3) R(4)-], cyclo [-R(1) R(2) Asp-D-Leu-D-Ala-D-Ala R(3) R(4)-], and



wherein R(1) R(2), R(3) and R(4) represent independently alanine, ornithine, cysteine, lysine, glutamic and aspartic acid, and wherein there is a covalent bond between the carboxyl and amino termini by which R(1) and R(4) are interconnected to each other via a methylene bridge of type $--(CH_2)_m--$ or $--(CH_2)_m--M--(CH_2)_{m'}--$, wherein m and m' are integers from 1, 2, 3, or 4, and M is NH, N[R(5)], O, or S, and wherein R(5) is methyl, ethyl, n-propyl, isopropyl, cyclopropyl, or cyclobutyl, or the sidechain of any naturally occurring amino acid, and a physiologically acceptable salt thereof and a peptidomimetic falling within the structure

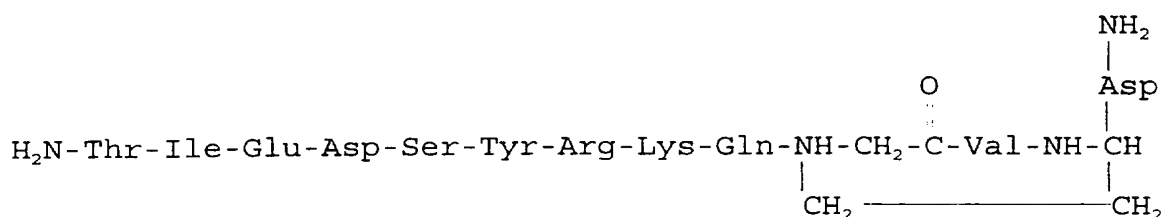


STRUCTURE 1

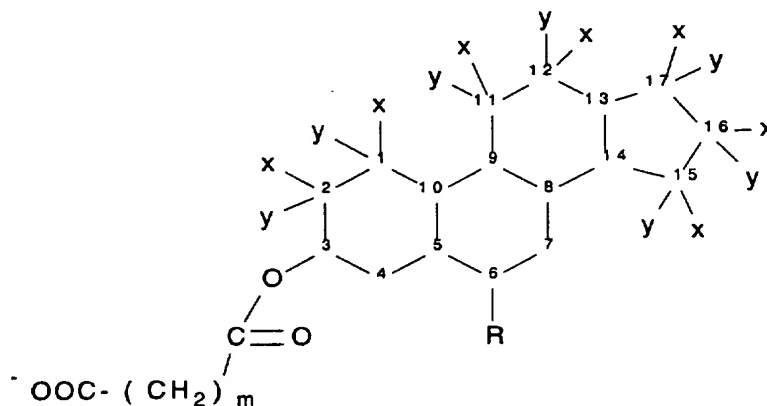
wherein the sidechain R attached at the carbon atom numbered 6 on the sterol nucleus can be $NH-CH_2-CH_2NH_3^+$, alkylamino, arylamino, or aralkylamino group, and wherein the sidechain attached at the carbon number 3 can be replaced with $-O-C(=O)--(CH_2)_m--COOH$, where m is an integer from 1 to 6, inclusive, preferably from 1 to 3, inclusive, and more preferably 2, and one of X and Y at each position independently, can be one H, a small alkyl group of C_1 to C_3 , preferably C_1 ; a halogen, preferably F, or an amino group where the other of one of X and Y is H. Preferably,

each of X and Y is H and a pharmaceutically acceptable salt thereof.

2. The composition of claim 1 wherein said component is a peptide has a structure having the structure



3. The composition of claim 1 wherein said peptidomimetic capable of inhibiting the oncogenic activity of p21 Ras has the structure

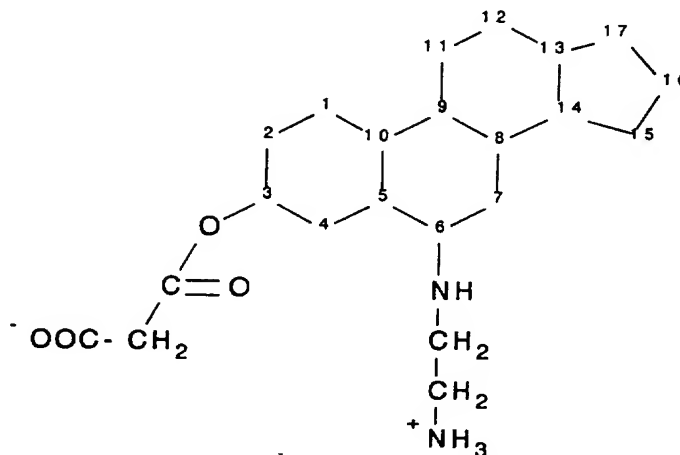


STRUCTURE 1

wherein the sidechain R attached at the carbon atom numbered 6 on the sterol nucleus can be NH-CH₂-CH₂NH₃⁺, alkylamino, arylamino, or aralkylamino group, and wherein the sidechain attached at the carbon number 3 can be replaced with -O-C(=O)--(CH₂)_m--COOH, where m is an integer from 1 to 6, inclusive, preferably from 1 to 3, inclusive, and more preferably 2, and one of X and Y at each position independently, can be one H, a small alkyl group of C₁ to C₃, preferably C₁; a halogen, preferably F, or an amino

group where the other of one of X and Y is H. Preferably, each of X and Y is H and a pharmaceutically acceptable salt thereof.

4. The composition of claim 1 wherein said peptidomimetic has the structure

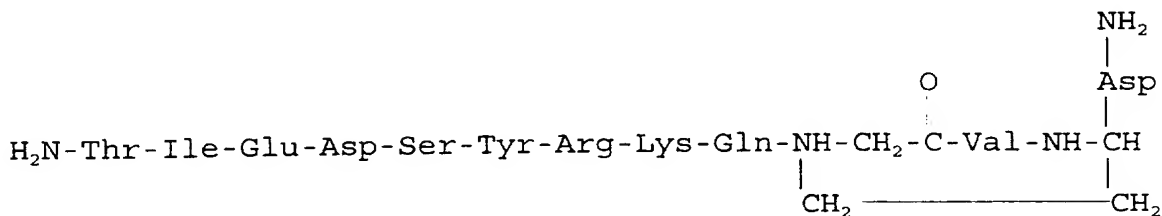


STRUCTURE 2

or a pharmaceutically acceptable salt thereof.

5. A method for inhibiting the oncogenic or transforming activity of p21 Ras, said method comprising the step of administering an amount of the composition of of claim 1 effective to achieve the result that the transforming and/or oncogenic activity of the p21 Ras protein is inhibited.
6. A method for inhibiting the oncogenic or transforming activity of p21 Ras, said method comprising the step of administering an amount of a composition comprising at least one cyclized peptide as set forth in claim 1, effective to achieve the result that the transforming and/or oncogenic activity of the p21 Ras protein is inhibited.

- 1 7. The method of claim 6 wherein the cyclized peptide has a
 2 structure



- 1 8. A method for inhibiting the oncogenic or transforming
 2 activity of p21 Ras, said method comprising the step of
 3 administering an effective amount of at least one
 4 peptidomimetic as set forth in claim 4, with the result
 5 that the transforming and/or oncogenic activity of the p21
 6 Ras protein is inhibited.

- 1 9. The method of claim 8 wherein said peptidomimetic is
 2 3-malonoxy-6-N-(2aminoethyl)
 3 aminocyclopentanoperhydrophenanthrene.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15098

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/00; C07K 5/12, 7/06, 7/08

US CL :530/317, 327, 329, 330; 514/14, 15, 16, 17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/317, 327, 329, 330; 514/14, 15, 16, 17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	Anticancer Research, Volume 11, No.4, issued 1991, Chung et al, "A Peptide from the GAP-Binding Domain of the ras-p21 Protein and Azatyrosine Block ras - Induced Maturation of Xenopus Oocytes", pages 1373-1378, especially page 1374.	1, 2, 5, 6 ----- 3, 4, 7-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

07 JANUARY 1997

Date of mailing of the international search report

29.01.97

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

S.G. Marshall

Telephone No. (703) 308-0196